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PTO/SB/05 (4/98)
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Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 C F R. § 1 53(b))

Attorney Docket No.	Mo-5998/LeA 34,074
First Inventor or Application Identifier	Klaus Raming et al
Title	GABA B RECEPTORS
Express Mail Label No.	EF080092618US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. [X] * Fee Transmittal Form *(e.g., PTO/SB/17)*
(Submit an original and a duplicate for fee processing)
2. [X] Specification [*Total Pages* 26]
(preferred arrangement set forth below)
   - Descriptive title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to Microfiche Appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
3. [X] Drawing(s) *(35 U.S.C. 113)* [*Total Sheets* 2]
4. Oath or Declaration [*Total Pages* 2]
   a. [X] Newly executed (original or copy)
   b. [ ] Copy from a prior application (37 C.F.R. § 1.63(d))
   (for continuation/divisional with Box 16 completed)
   i [ ] DELETION OF INVENTOR(S)
   Signed statement attached deleting inventor(s) named in the prior application, see 37 C F.R. §§ 1 63(d)(2) and 1 33(b).

** NOTE FOR ITEMS 1 & 13 IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).*

ADDRESS TO: **Assistant Commissioner for Patents**
Box Patent Application
Washington, DC 20231

5. [ ] Microfiche Computer Program *(Appendix)*
6. Nucleotide and/or Amino Acid Sequence Submission
(if applicable, all necessary)
   a. [X] Computer Readable Copy
   b. [X] Paper Copy (identical to computer copy)
   c. [X] Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

7. [X] Assignment Papers (cover sheet & document(s))
8. [ ] 37 C.F.R.§3.73(b) Statement *(when there is an assignee)* [ ] Power of Attorney
9. [ ] English Translation Document *(if applicable)*
10. [ ] Information Disclosure Statement (IDS)/PTO-1449 [ ] Copies of IDS Citations
11. [X] Preliminary Amendment
12. [X] Return Receipt Postcard (MPEP 503)
(Should be specifically itemized)
13. [ ] * Small Entity Statement(s) *(PTO/SB/09-12)* [ ] Statement filed in prior application Status still proper and desired
14. [X] Certified Copy of Priority Document(s)
(if foreign priority is claimed)
15. [ ] Other:

16. If a **CONTINUING APPLICATION,** *check appropriate box, and supply the requisite information below and in a preliminary amendment:*

[ ] Continuation [ ] Divisional [ ] Continuation-in-part (CIP) of prior application No _____/_____

Prior application information: *Examiner* _____ *Group / Art Unit:* _____

For CONTINUATION or DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 4b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

17. CORRESPONDENCE ADDRESS

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Name (Print/Type)	Joseph C. Gil	*Registration No. (Attorney/Agent)*	26,602
Signature		*Date*	11/17/00

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FEE TRANSMITTAL for FY 2000

Patent fees are subject to annual revision
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See 37 C F R §§ 1 27 and 1 28.

TOTAL AMOUNT OF PAYMENT ($) 1,182.00

Complete if Known	
Application Number	To be Assigned
Filing Date	Herewith
First Named Inventor	Klaus Raming et al
Examiner Name	--
Group / Art Unit	--
Attorney Docket No.	Mo-5998/LeA 34,074

METHOD OF PAYMENT (check one)

1. [X] The Commissioner is hereby authorized to charge indicated fees and credit any overpayments to:

Deposit Account Number: 13-3848

Deposit Account Name: Bayer Corporation

[X] Charge Any Additional Fee Required Under 37 CFR §§ 1 16 and 1 17

2. [ ] **Payment Enclosed:** [ ] Check [ ] Money Order [ ] Other

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	690	201	345	Utility filing fee	710.00
106	310	206	155	Design filing fee	
107	480	207	240	Plant filing fee	
108	690	208	345	Reissue filing fee	
114	150	214	75	Provisional filing fee	

SUBTOTAL (1) ($) 710.00

2. EXTRA CLAIM FEES

			Extra Claims		Fee from below		Fee Paid
Total Claims	29	-20** =	9	X	18	=	162
Independent Claims	2	- 3** =	0	X	80	=	0
Multiple Dependent					270	=	270

***or number previously paid, if greater, For Reissues, see below*

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	18	203	9	Claims in excess of 20
102	78	202	39	Independent claims in excess of 3
104	260	204	130	Multiple dependent claim, if not paid
109	78	209	39	** Reissue independent claims over original patent
110	18	210	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 432.00

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	0.00
127	50	227	25	Surcharge - late provisional filing fee or cover sheet.	0.00
139	130	139	130	Non-English specification	0.00
147	2,520	147	2,520	For filing a request for reexamination	0.00
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	0.00
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	0.00
115	110	215	55	Extension for reply within first month	0.00
116	380	216	190	Extension for reply within second month	0.00
117	870	217	435	Extension for reply within third month	0.00
118	1,360	218	680	Extension for reply within fourth month	0.00
128	1,850	228	925	Extension for reply within fifth month	0.00
119	300	219	150	Notice of Appeal	0.00
120	300	220	150	Filing a brief in support of an appeal	0.00
121	260	221	130	Request for oral hearing	0.00
138	1,510	138	1,510	Petition to institute a public use proceeding	0.00
140	110	240	55	Petition to revive - unavoidable	0.00
141	1,210	241	605	Petition to revive - unintentional	0.00
142	1,210	242	605	Utility issue fee (or reissue)	0.00
143	430	243	215	Design issue fee	0.00
144	580	244	290	Plant issue fee	0.00
122	130	122	130	Petitions to the Commissioner	0.00
123	50	123	50	Petitions related to provisional applications	0.00
126	240	126	240	Submission of Information Disclosure Stmt	0.00
581	40	581	40	Recording each patent assignment per property (times number of properties)	40.00
146	690	246	345	Filing a submission after final rejection (37 CFR § 1.129(a))	0.00
149	690	249	345	For each additional invention to be examined (37 CFR § 1.129(b))	0.00
Other fee (specify)					0.00
Other fee (specify)					0.00

* Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 40.00

SUBMITTED BY

				Complete *(if applicable)*	
Name (Print/Type)	Joseph C. Gil	*Registration No. (Attorney/Agent)*	26,602	*Telephone*	777-2342
Signature				*Date*	11/17/00

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PATENT APPLICATION
Mo-5998
LeA 34,074

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICATION OF)
)
KLAUS RAMING ET AL.)
)
SERIAL NUMBER: TO BE ASSIGNED)
)
FILED: HEREWITH)
)
TITLE: GABA B RECEPTORS)

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington D.C. 20231
Sir:

Upon the granting of a Serial Number and Filing date and prior to the examination of the subject application, kindly amend the application as follows.

IN THE SPECIFICATION:

On page 1, between lines 5 and 6, please insert -- BACKGROUND OF THE INVENTION --.

On page 2, before line 2, please insert -- BRIEF SUMMARY OF THE INVENTION --.

On page 3, before line 2, please insert -- DETAILED DESCRIPTION OF THE INVENTION --.

"Express Mail" mailing label number EF080092618US
Date of Deposit November 17, 2000

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner of Patents and Trademarks, Washington, D.C. 20231

Donna J. Veatch
(Name of person mailing paper or fee)

(Signature of person mailing paper or fee)

On page 7, line 4, following "the main operator and promoter regions of", please delete "phase" and insert -- phage --.

On page 21, line 1, please delete "Patent Claims" and insert -- WHAT IS CLAIMED IS: --.

IN THE CLAIMS:

Please amend Claims 1 - 8 as follows:

1. (Amended) A purified and isolated [P]polypeptide [which exerts] having the biological activity of a GABA B receptor and [which comprises] comprising an amino acid sequence which has at least 70% identity with a sequence of SEQ ID NO: 2, SEQ ID NO: 4 or SEQ ID NO: 6.

2. (Amended) The [P]polypeptide according to Claim 1, characterized in that the amino acid sequence corresponds to a sequence of SEQ ID NO: 2, SEQ ID NO: 4 or SEQ ID NO: 6.

3. (Amended) A purified and isolated [N]nucleic acid comprising a nucleotide sequence which encodes a polypeptide according to Claim 1.

4. (Amended) The [N]nucleic acid according to Claim 3, characterized in that it is a single- or double-stranded DNA or RNA.

5. (Amended) The [N]nucleic acid according to Claim 4, characterized in that it is a fragment of genomic DNA or cDNA.

6. (Amended) The [N]nucleic acid according to Claim 3, characterized in that the nucleotide sequence corresponds to a sequence of SEQ ID NO: 1, SEQ ID NO: 3 or SEQ ID NO: 5.

7. (Amended) The [N]nucleic acid according to Claim 3, characterized in that it hybridizes under stringent conditions to the sequences of SEQ ID NO: 1, SEQ ID NO: 3 or SEQ ID NO: 5.

8. (Amended) A DNA construct comprising a nucleic acid according to [any of] Claim[s] 3 [to 7] and a heterologous promoter.

Please cancel Claim 9.

Please amend Claims 10 -17 as follows:

10. (Amended) A vector [according to Claim 9], characterized in that the nucleic acid of Claim 3 is [operatively] linked to regulatory sequences which ensure the expression of the nucleic acid in pro-karyotic or eukaryotic cells.

11. (Amended) A [H]host cell [containing] stably transformed or transfected with a nucleic acid according to [any of] Claim[s] 3 [to 7, a DNA construct according to Claim 8 or a vector according to Claim 9 or 10].

12. (Amended) The [H]host cell according to Claim 11, which is a prokaryotic cell[, in particular E. coli].

13. (Amended) A [H]host cell according to Claim 11, which is a eukaryotic cell[, in particular a mammalian or insect cell].

14. (Amended) An [A]antibody substance which binds specifically to a polypeptide according to Claim 1.

15. (Amended) A [T]transgenic invertebrate containing a nucleic acid according to [any of] Claim[s] 3 [to 7].

16. (Amended) The [T]transgenic invertebrate according to Claim 15, which is Drosophila melanogaster or Caenorhabditis elegans.

17. (Amended) The [T]transgenic progeny of an invertebrate according to Claim 15 [or 16].

Please cancel Claims 18, 19, 20, 21, 22, 23, 24 and 25.

Please add Claims 26 - 38 as follows:

-- 26. A vector comprising a nucleic acid according to Claim 3 or the nucleic acid of Claim 3 and a heterologous promoter.

27. The host cell of Claim 11 containing a DNA construct according to Claim 8.

28. The host cell of Claim 11 containing a vector according to Claim 10.

29. The host cell of Claim 11 wherein the prokaryotic cell is E. coli.

30. The host cell of Claim 11 wherein the eukaryotic cell is a mammalian or insect cell.

31. A method of generating a polypeptide having the biological activity of a GABA B receptor and comprising an amino acid sequence which has at least 70% identity with a sequence of SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:6, comprising

a) culturing a host cell stably transformed or transfected with a nucleic acid according to Claim 3 under conditions which ensure the expression of the nucleic acid according to Claim 3, or

b) expressing a nucleic acid according to Claim 3 in an in-vitro system, and

(c) obtaining the polypeptide from the cell, the culture medium or the in-vitro system.

32. A method of generating a nucleic acid according to Claim 3, comprising the steps selected from the group consisting of:

(a) full chemical synthesis in a manner known per se,

(b) chemical synthesis of oligonucleotides further comprising, labelling of the oligonucleotides, hybridizing the oligonucleotides to DNA of a genomic library or cDNA library generated from insect genomic DNA or insect mRNA, respectively, and selecting positive clones and isolating the hybridizing DNA from positive clones, and

(c) chemical synthesis of oligonucleotides and amplification of the target DNA by PCR.

33. A method of generating a transgenic invertebrate, comprising stably transforming or transfecting an invertebrate cell or organism with a nucleic acid selected from the group consisting of a nucleic acid of Claim 3, a nucleic acid of Claim 3 and a heterologous promoter, and a vector comprising a nucleic acid of Claim 3 operatively linked to regulatory sequences ensuring expression of the nucleic acid of Claim 3 in the invertebrate cell or organism.

34. A method of finding new active compounds for crop protection which alter the properties of polypeptides having the biological activity of a GABA B receptor and comprising an amino acid sequence which has at least 70% identity with a sequence of SEQ ID NO: 2, SEQ ID NO: 4 or SEQ ID NO: 6, comprising the steps of:

a) providing a host cell according to Claim 11,

b) culturing the host cell in the presence of a chemical or of a sample comprising a multiplicity of chemicals, and

(c) detecting altered properties .

35. A method of finding a chemical which binds to a polypeptide having the biological activity of a GABA B receptor and comprising an amino acid sequence which has at least 70% identity with a sequence of SEQ ID NO: 2, SEQ ID NO: 4 or SEQ ID NO: 6, comprising the steps of:

(a) contacting a polypeptide according to Claim 1 or a host cell according to Claim 11 with a chemical or a mixture of chemicals under conditions which permit the interaction of a chemical with the polypeptide, and

(b) determining the chemical which binds specifically to the polypeptide.

36. A method of finding a chemical which alters the expression of a polypeptide having the biological activity of a GABA B receptor and comprising an amino acid sequence which has at least 70% identity with a sequence of SEQ ID NO: 2, SEQ ID NO: 4 or SEQ ID NO: 6, comprising the steps of :

(a) contacting a host cell according to Claim 11 or a transgenic invertebrate according to Claim 15 with a chemical or a mixture of chemicals,

(b) determining the concentration of the polypeptide according to Claim 1, and

(c) determining the chemical which specifically affects the expression of the polypeptide.

37. A method of finding new active compounds for crop protection or for finding genes which encode polypeptides which participate in the synthesis of functionally similar GABA B receptors in insects comprising selecting for said active compounds with a bio-molecule, cell, or organism selected from the group consisting of:

(a) a polypeptide according to Claim 1,

(b) a nucleic acid according to Claim 3,

(c) a vector according to Claim 26,

(d) a host cell according to Claim 11,

(e) an antibody substance according to Claim 14; and

(f) a transgenic invertebrate according to Claim 15.

38. A method of killing insect pests comprising applying a modulator of a polypeptide according to Claim 1. --

REMARKS

The Claims have been amended to put them in a form more commonly used for US filing. Claims 1 to 17 have been amended as to form and to remove multiple dependencies. Claim 9 has been cancelled and rewritten as Claim 26. Claim 11 has been amended to remove multiple dependent form and Claims 27 to 30 added to claim the dependent subject matter. Claims 18 and 19 have been cancelled and rewritten as Claims 31 and 32. Claims 20, 21, 22 and 23 have been cancelled and rewritten as Claim 33, 34, 35, and 36. Claims 24 and 25 have been cancelled and rewritten as Claims 37 and 38.

Applicants attach hereto the Sequence Listing in the form of a Computer readable Copy and Paper Copy. Applicants by their Attorney state that the contents of the Computer Readable Copy and Paper Copy are the same and no new matter has been added.

An action on the merits is respectfully requested.

Respectfully submitted,

KLAUS RAMING
MARIO MEZLER
THOMAS MÜLLER

By _____
Joseph C. Gil
Attorney for Applicants
Reg. No. 26,602

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s:\ksl\JA0057

GABA B receptors

The invention relates to polypeptides which exert the biological activity of GABA B receptors and to nucleic acids encoding these polypeptides, and, in particular, to their use for finding active compounds for crop protection.

Gamma-amino-butyric acid (GABA) is the most important inhibitory neurotransmitter in the nervous system of vertebrates and invertebrates. The GABA receptors can be classified into two subfamilies, the GABA A and GABA B receptors. Amongst these, the GABA A receptors are ligand-controlled ion channels, while the GABA B receptors are metabotropic, G-protein-coupled receptors. GABA B receptors affect the release of various neurotransmitters and the activity of ion channels.

GABA B receptors have been studied extensively, in particular in vertebrates. Two subtypes (GABA B1 and GABA B2), which are functionally active as heterodimers, are known here (Jones et al., 1998; Kaupmann et al., 1998; White et al., 1998).

In insects, GABA is the most important inhibitory neurotransmitter of the central nervous system. Accordingly, GABA receptors can be detected electrophysiologically on preparations of insect central ganglia. Both the GABA A receptors and the GABA B receptors are the molecular target of important natural and synthetic insecticidally active compounds (Sattelle, 1990; Fukunaga et al., 1999).

The protein sequence of a number of insect GABA A receptors is already known. Thus, the sequences of three different subunits have been described for Drosophila melanogaster (ffrench-Constant et al., 1991; Harvey et al., 1994; Henderson et al., 1993).

The provision of insect GABA B receptors is therefore of great practical importance, for example in the search for new insecticides.

The present invention is therefore based in particular on the object of providing insect GABA B receptors and on assay systems based thereon with a high throughput of test compounds (high throughput screening assays; HTS assays).

The object is achieved by providing polypeptides which exert at least one biological activity of a GABA B receptor and which comprise an amino acid sequence having at least 70% identity, preferably at least 80% identity, especially preferably at least 90% identity, very especially preferably at least 95% identity, with a sequence of SEQ ID NO: 2, SEQ ID NO: 4 or SEQ ID NO: 6 over a length of at least 20, preferably at least 25, especially preferably at least 30 consecutive amino acids, and very especially preferably over their full lengths.

The degree of identity of the amino acid sequences is preferably determined using the program GAP from the package GCG, Version 9.1, with standard settings (Devereux et al., 1984).

The term "polypeptides" as used in the present context not only relates to short amino acid chains which are usually termed peptides, oligopeptides or oligomers, but also to longer amino acid chains which are usually termed proteins. It encompasses amino acid chains which can be modified either by natural processes, such as post-translational processing, or by chemical prior-art methods. Such modifications may occur at various sites and repeatedly in a polypeptide, such as, for example, on the peptide backbone, on the amino acid side chain, on the amino and/or the carboxyl terminus. For example, they encompass acetylations, acylations, ADP-ribosylations, amidations, covalent linkages to flavins, haem-moieties, nucleotides or nucleotide derivatives, lipids or lipid derivatives or phosphatidylinositol, cyclizations, di-sulphide bridge formations, demethylations, cystine formations, formylations, gamma-carboxylations, glycosylations, hydroxylations, iodinations, methylations, myristylations, oxidations, proteolytic processings, phosphorylations, selenylations and tRNA-mediated amino acid additions.

The polypeptides according to the invention may exist in the form of "mature" proteins or parts of larger proteins, for example as fusion proteins. They can furthermore exhibit secretion or leader sequences, pro-sequences, sequences which allow simple purification, such as multiple histidine residues, or additional stabilizing amino acids.

The biological activity of the GABA B receptors is preferably achieved by hetero-dimerization of the polypeptides according to the invention. For example, the polypeptides according to the invention with an amino acid sequence of SEQ ID NO: 2 and SEQ ID NO: 4, SEQ ID NO: 2 and SEQ ID NO: 6 or SEQ ID NO: 4 and SEQ ID NO: 6 can gain receptor activity by dimerization.

The polypeptides according to the invention need not constitute complete receptors, but may also be fragments thereof, as long as they still have at least one biological activity of the complete receptors. Polypeptides which, compared with GABA B receptors, are composed of the polypeptides according to the invention with an amino acid sequence of SEQ ID NO: 2 and SEQ ID NO: 4, which have a 50% higher or reduced activity, are still considered to be in accordance with the invention. The polypeptides according to the invention need not be deducible from Drosophila melanogaster GABA B receptors. Polypeptides which are also considered as being in accordance with the invention are those which correspond to the GABA B receptors of, for example, the following invertebrates, or fragments thereof which can still exert the biological activity of these receptors: arthropods, nematodes, molluscs.

In comparison with the corresponding region of naturally occurring GABA B receptors, the polypeptides according to the invention can have deletions or amino acid substitutions, as long as they still exert at least one biological activity of the complete receptors. Conservative substitutions are preferred. Such conservative substitutions encompass variations, one amino acid being replaced by another amino acid from amongst the following group:

1. small aliphatic residues, unpolar residues or residues of little polarity: Ala, Ser, Thr, Pro and Gly;
2. polar, negatively charged residues and their amides: Asp, Asn, Glu and Gln;
3. polar, positively charged residues: His, Arg and Lys;
4. large aliphatic unpolar residues: Met, Leu, Ile, Val and Cys; and
5. aromatic residues: Phe, Tyr and Trp.

Preferred conservative substitutions can be seen from the following list:

Original residue	**Substitution**
Ala	Gly, Ser
Arg	Lys
Asn	Gln, His
Asp	Glu
Cys	Ser
Gln	Asn
Glu	Asp
Gly	Ala, Pro
His	Asn, Gln
Ile	Leu, Val
Leu	Ile, Val
Lys	Arg, Gln, Glu
Met	Leu, Tyr, Ile
Phe	Met, Leu, Tyr
Ser	Thr
Thr	Ser
Trp	Tyr
Tyr	Trp, Phe
Val	Ile, Leu

The term "biological activity of a GABA B receptor" as used in the present context means binding GABA.

Preferred embodiments of the polypeptides according to the invention are Drosophila melanogaster GABA B receptors which have the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 4 or SEQ ID NO: 6.

Subject-matter of the present invention are also nucleic acids which encode the polypeptides according to the invention.

The nucleic acids according to the invention are, in particular, single-stranded or double-stranded deoxyribonucleic acids (DNA) or ribonucleic acids (RNA). Preferred embodiments are fragments of genomic DNA which may contain introns, and cDNAs.

cDNAs which have a nucleotide sequence of SEQ ID NO: 1, SEQ ID NO: 3 or SEQ ID NO: 5 constitute preferred embodiments of the nucleic acids according to the invention.

The present invention also encompasses nucleic acids which hybridize under stringent conditions with sequences of SEQ ID NO: 1, SEQ ID NO: 3 or SEQ ID NO: 5.

The term "to hybridize" as used in the present context describes the process during which a single-stranded nucleic acid molecule undergoes base pairing with a complementary strand. Starting from the sequence information disclosed herein, this allows, for example, DNA fragments to be isolated from insects other than Drosophila melanogaster which encode polypeptides with the biological activity of GABA B receptors.

Preferred hybridization conditions are stated hereinbelow:

Hybridization solution: 6X SSC / 0 % formamide, preferred hybridization solution: 6X SSC / 25 % formamide

Hybridization temperature: 34°C, preferred hybridization temperature: 42°C

Wash step 1: 2X SSC at 40°C,
Wash step 2: 2X SSC at 45°C; preferred wash step 2: 0.6X SSC at 55°C, especially preferred wash step 2: 0.3 X SSC at 65°C.

The present invention encompasses furthermore nucleic acids which have at least 70% identity, preferably at least 80% identity, especially preferably at least 90% identity, very especially preferably at least 95% identity, with a sequence of SEQ ID NO: 1, SEQ ID NO: 3 or SEQ ID NO: 5 over a length of at least 20, preferably at least 25, especially preferably at least 30, consecutive nucleotides, and very especially preferably over their full lengths.

The degree of identity of the nucleic acid sequences is preferably determined with the aid of program GAP from the package GCG, Version 9.1, using standard settings.

The sequences in accordance with the GenBank accession numbers (Acc. No.) AC002502, AF145639 and AC004420 are incorporated into the present description by reference.

Subject-matter of the present invention are furthermore DNA constructs which comprise a nucleic acid according to the invention and a heterologous promoter.

The term "heterologous promoter" as used in the present context refers to a promoter which has properties other than the promoter which controls the expression of the gene in question in the original organism. The term "promoter" as used in the present context generally refers to expression control sequences.

The choice of heterologous promoters depends on whether pro- or eukaryotic cells or cell-free systems are used for expression. Examples of heterologous promoters are the SV40, the adenovirus or the cytomegalovirus early or late promoter, the lac system, the trp system, the main operator and promoter regions of phase lambda, the fd coat protein control regions, the 3-phosphoglycerate kinase promoter, the acid phosphatase promoter and the yeast α-mating factor promoter.

Subject-matter of the present invention are furthermore vectors which contain a nucleic acid according to the invention or a DNA construct according to the invention. All the plasmids, phasmids, cosmids, YACs or artificial chromosomes used in molecular biology laboratories can be used as vectors.

Subject-matter of the present invention are also host cells comprising a nucleic acid according to the invention, a DNA construct according to the invention or a vector according to the invention.

The term "host cell" as used in the present context refers to cells which do not naturally comprise the nucleic acids according to the invention.

Suitable host cells are prokaryotic cells such as bacteria from the genera Bacillus, Pseudomonas, Streptomyces, Streptococcus, Staphylococcus, preferably E. coli, but also eukaryotic cells such as yeasts, mammalian cells, amphibian cells, insect cells or plant cells. Preferred eukaryotic host cells are HEK-293, Schneider S2, Spodoptera Sf9, Kc, CHO, COS1, COS7, HeLa, C127, 3T3 or BHK cells and, in particular, Xenopus oocytes.

Another subject-matter of the invention are antibodies which specifically bind to the abovementioned polypeptides or receptors. Such antibodies are produced in the customary manner. For example, such antibodies may be produced by injecting a substantially immunocompetent host with such an amount of a polypeptide according to the invention or a fragment thereof which is effective for antibody production, and

subsequently obtaining this antibody. Furthermore, an immortalized cell line which produces monoclonal antibodies may be obtained in a manner known per se. If appropriate, the antibodies may be labelled with a detection reagent. Preferred examples of such a detection reagent are enzymes, radiolabelled elements, fluorescent chemicals or biotin. Instead of the complete antibody, fragments may also be employed which have the desired specific binding properties. The term "antibodies" as used in the present context therefore also extends to parts of complete antibodies, such as Fa, $F(ab')_2$ or Fv fragments, which are still capable of binding to the epitopes of the polypeptides according to the invention.

The nucleic acids according to the invention can be used, in particular, for generating transgenic invertebrates. These may be employed in assay systems which are based on an expression, of the polypeptides according to the invention, which deviates from the wild type. Based on the information disclosed herein, it is furthermore possible to generate transgenic invertebrates where expression of the polypeptides according to the invention is altered owing to the modification of other genes or promoters.

The transgenic invertebrates are generated, for example, in the case of Drosophila melanogaster, by P-element-mediated gene transfer (Hay et al., 1997), or, in Caenorhabditis elegans, by transposon-mediated gene transfer (for example by Tc1; Plasterk, 1996).

Subject-matter of the invention are therefore also transgenic invertebrates which contain at least one of the nucleic acids according to the invention, preferably transgenic invertebrates of the species Drosophila melanogaster or Caenorhabditis elegans, and their transgenic progeny. The transgenic invertebrates preferably contain the polypeptides according to the invention in a form which deviates from the wild type.

Subject-matter of the present invention are furthermore processes for producing the polypeptides according to the invention. To produce the polypeptides encoded by the

nucleic acids according to the invention, host cells which contain one of the nucleic acids according to the invention can be cultured under suitable conditions, where the nucleic acid to be expressed may be adapted to the codon usage of the host cells. Thereupon, the desired polypeptides can be isolated from the cells or the culture medium in the customary manner. The polypeptides may also be produced in *in vitro* systems.

A rapid method of isolating the polypeptides according to the invention which are synthesized by host cells using a nucleic acid according to the invention starts with the expression of a fusion protein, it being possible for the fusion partner to be affinity-purified in a simple manner. For example, the fusion partner may be glutathione S-transferase. The fusion protein can then be purified on a glutathione affinity column. The fusion partner can then be removed by partial proteolytic cleavage, for example at linkers between the fusion partner and the polypeptide according to the invention to be purified. The linker can be designed such that it includes target amino acids such as arginine and lysine residues, which define sites for trypsin cleavage. To generate such linkers, standard cloning methods using oligonucleotides may be employed.

Other purification methods which are possible are based on preparative electrophoresis, FPLC, HPLC (for example using gel filtration, reversed-phase or moderately hydrophobic columns), gel filtration, differential precipitation, ion-exchange chromatography and affinity chromatography.

Since GABA B receptors constitute membrane proteins, the purification methods preferably involve detergent extractions, for example using detergents which have no, or little, effect on the secondary and tertiary structures of the polypeptides, such as nonionic detergents.

The purification of the polypeptides according to the invention can encompass the isolation of membranes, starting from host cells which express the nucleic acids according to the invention. Such cells preferably express the polypeptides according to

the invention in a sufficiently high copy number, so that the polypeptide quantity in a membrane fraction is at least 10 times higher than that in comparable membranes of cells which naturally express GABA B receptors; especially preferably, the quantity is at least 100 times, very especially preferably at least 1000 times higher.

The terms "isolation or purification" as used in the present context mean that the polypeptides according to the invention are separated from other proteins or other macromolecules of the cell or of the tissue. The protein content of a composition containing the polypeptides according to the invention is preferably at least 10 times, especially preferably at least 100 times, higher than in a host cell preparation.

The polypeptides according to the invention may also be affinity-purified without a fusion partner with the aid of antibodies which bind to the polypeptides.

Another subject-matter of the present invention are processes for the generation of the nucleic acids according to the invention. The nucleic acids according to the invention can be generated in the customary manner. For example, all of the nucleic acid molecules can be synthesized chemically, or else only short sections of the sequences according to the invention can be synthesized chemically, and such oligonucleotides can be radiolabelled or labelled with a fluorescent dye. The labelled oligonucleotides can be used for screening cDNA libraries generated starting from insect mRNA or for screening genomic libraries generated starting from insect genomic DNA. Clones which hybridize with the labelled oligonucleotides are chosen for isolating the DNA in question. After characterization of the DNA which has been isolated, the nucleic acids according to the invention are obtained in a simple manner.

Alternatively, the nucleic acids according to the invention can also be generated by means of PCR methods using chemically synthesized oligonucleotides.

The term "oligonucleotide(s)" as used in the present context denotes DNA molecules composed of 10 to 50 nucleotides, preferably 15 to 30 nucleotides. They are synthesized chemically and can be used as probes.

The nucleic acids or polypeptides according to the invention allow new active compounds for crop protection and/or pharmaceutical active compounds for the treatment of humans and animals to be identified, such as chemical compounds which, being modulators, in particular agonists or antagonists, alter the properties of the GABA B receptors according to the invention. To this end, a recombinant DNA molecule comprising at least one nucleic acid according to the invention is introduced into a suitable host cell. The host cell is grown in the presence of a compound or a sample comprising a variety of compounds under conditions which allow expression of the receptors according to the invention. A change in the receptor properties can be detected for example as described hereinbelow in Example 2. This allows, for example, insecticidal substances to be found.

GABA B receptors alter the concentration of intracellular cAMP via interaction with G proteins, preferably after previously having been activated. Thus, changes in the receptor properties by chemical compounds can be measured after heterologous expression, for example by measuring the intracellular cAMP concentrations directly via ELISA assay systems (Biomol, Hamburg, Germany) or RIA assay systems (NEN, Schwalbach, Germany) in HTS format. An indirect measurement of the cAMP concentration is possible with the aid of reporter genes (for example luciferase), whose expression depends on the cAMP concentration (Stratowa et al., 1995). The coexpression of GABA B receptors with specific G proteins, for example Gα15, Gα15 or else chimeric G proteins, in heterologous systems and measuring the rise in calcium, for example using fluorescent dyes or equorin, is an alternative possibility of carrying out the screening (Stables et al., 1997; Conklin et al., 1993).

Furthermore, the binding of GTP to the activated G protein can be used as a read-out-system for assaying substances. Also, binding experiments with labelled GABA can be employed for screening.

The term "agonist" as used in the present context refers to a molecule which activates GABA B receptors.

The term "antagonist" as used in the present context refers to a molecule which displaces an agonist from its binding site.

The term "modulator" as used in the present invention constitutes the generic term for agonist and antagonist. Modulators can be small organochemical molecules, peptides or antibodies which bind to the polypeptides according to the invention. Other modulators may be small organochemical molecules, peptides or antibodies which bind to a molecule which, in turn, binds to the polypeptides according to the invention, thus affecting their biological activity. Modulators may constitute mimetics of natural substrates and ligands.

The modulators are preferably small organochemical compounds.

The binding of the modulators to the polypeptides according to the invention can alter the cellular processes in a manner which leads to the death of the insects treated therewith.

The present invention therefore also extends to the use of modulators of the polypeptides according to the invention as insecticides.

The nucleic acids or polypeptides according to the invention also allow compounds to be found which bind to the receptors according to the invention. Again, they can be applied to plants as insecticides. For example, host cells which contain the nucleic acids according to the invention and which express the corresponding receptors or

polypeptides, or the gene products themselves, are brought into contact with a compound or a mixture of compounds under conditions which permit the interaction of at least one compound with the host cells, the receptors or the individual polypeptides.

Using host cells or transgenic invertebrates which contain the nucleic acids according to the invention, it is also possible to find substances which alter receptor expression.

The above-described nucleic acids according to the invention, vectors and regulatory regions can furthermore be used for finding genes which encode polypeptides which participate in the synthesis, in insects, of functionally similar GABA B receptors. Functionally similar receptors are to be understood as meaning in accordance with the present invention receptors which comprise polypeptides which, while differing from the amino acid sequence of the polypeptides described herein, essentially have the same functions.

Information on the sequence listing and the figures

SEQ ID NO: 1, SEQ ID NO: 3 and SEQ ID NO: 5 show the nucleotide and amino acid sequences of the isolated GABA B cDNAs. SEQ ID NO: 2, SEQ ID NO: 4 and SEQ ID NO: 6 furthermore show the amino acid sequences of the proteins deduced from the GABA B cDNA sequences.

Figure 1 shows a dose-effect curve of GABA and 3-APMPA on the Drosophila GABA B receptor composed of the polypeptides according to the invention with the amino acid sequences of SEQ ID NO: 2 and SEQ ID NO: 4, expressed in Xenopus oocytes.

Figure 2 shows the functional coupling to the intracellular cAMP system of the coexpressed D-GABA B receptors R1/R2 composed of the polypeptides according to the invention with the amino acid sequences of SEQ ID NO: 2 and SEQ ID NO: 4.

HEK293 luc cells which have been stably transfected with D-GABA B R1/R2 (D-GABA R1/2) and untransfected control cells (control) were stimulated with forskolin, forskolin and GABA, and also with GABA alone, and the intracellular cAMP concentration was measured. The D-GABA B-R1/2-transfected cells showed a marked reduction in forskolin-induced cAMP response, while the control cells were unresponsive.

Examples

Example 1

Isolation of the above-described polynucleotide sequences

Polynucleotides were manipulated by standard methods of recombinant DNA technology (Sambrook et al., 1989). Nucleotide and protein sequences were processed in terms of bioinformatics using the package GCG Version 9.1 (GCG Genetics Computer Group, Inc., Madison Wisconsin, USA).

Example 2

Generation of the expression constructs

The sequence regions of SEQ ID NO: 1, SEQ ID NO: 3 and SEQ ID NO: 5 were amplified by means of polymerase chain reaction (PCR) and cloned into the vector pcDNA3.1/Neo (Invitrogen, Groningen).

Heterologous expression

HEK293 cells were cultured at 5% CO_2 and 37°C in Dulbecco's modified Eagle's medium and 10% foetal calf serum. MBS (Stratagene, La Jolla, USA) was used for the gene transfer, following the manufacturer's instructions. 24 h to 48 h after the gene transfer, the cells were sown intro microtiter plates at various densities. Recombinant cells were selected over 3 to 4 weeks by growth in Dulbecco's modified Eagles medium and 10% foetal calf serum and 700 µg/ml Geneticin (G418, Life Technologies, Karlsruhe) as selection marker. Individual resistant clones were analysed as described below.

Insect GABA B receptors were also expressed functionally in Xenopus oocytes. To this end, G-protein-activatable potassium channels (GIRK1 and GIRK4) were coexpressed in order to measure activation of the GABA B receptors (White et al., 1998).

cAMP measurements

HEK293 cell strains were used for determining the cAMP concentration. On the one hand, HEK293 cells stably coexpressed the two Drosophila melanogaster receptors D-GABA B R1 and D-GABA B R2 (D-GABA R1/2). On the other hand, untransfected control cells were incorporated into the assay (control). In each case, the cells were plated into 96-well-plates at a density of 20,000 cells per cavity. Control cells were incubated in culture medium (DMEM, 10% FCS, penicillin and streptomycin, 50 U/ml and 50 µg/ml (Life Technologies)) and D-GABA-R1/2 expressing cells in selection medium (culture medium with 0.5 mg/ml Geneticin (G418, Life Technologies)) for 48 hours at 37°C until a cell density of approximately 80% was reached. Thereupon, the medium was removed, and the cells were washed once with unsupplemented DMEM. After incubation for 30 minutes with IBMX (300 µM) at 37°C, cells were stimulated for 30 minutes with GABA (100 µM) and/or forskolin (10 µM) at 37°C. All incubation steps were carried out in unsupplemented DMEM (Life Technologies). Then, the stimulation medium was removed and the cells were lysed with 50 µl of HCl (0.1 N) per cavity. The cells were lysed for 20 minutes at room temperature with shaking, and the cAMP concentration of the cell lysates were determined in triplicate using the enzyme immunoassay (EIA) kit AK-200 (Biomol, Hamburg, Germany) following the manufacturer's description.

Oocyte measurements

1. Oocyte preparation

The oocytes were obtained from an adult female Xenopus laevis frog (Horst Kähler, Hamburg, Germany). The frogs were kept in large tanks with circulating water at a water temperature of 20 - 24°C. Parts of the frog ovary were removed through a small incision in the abdomen (approx. 1 cm), with full anaesthesia. The ovary was then treated for approximately 140 minutes with 25 ml collagenase (type I, C-0130, SIGMA-ALDRICH CHEMIE GmbH, Deisenhofen, Germany; 355 U/ml, prepared with Barth's solution without calcium in mM: NaCl 88, KCl 1, $MgSO_4$ 0.82, $NaHCO_3$ 2.4, Tris/HCl 5, pH7.4), with constant shaking. Then, the oocytes were washed with Barth's solution without calcium. Only oocytes at maturity stage V (Dumont, 1972) were selected for the further treatment and transferred into microtiter plates (Nunc MicroWell™ plates, cat. No. 245128 + 263339 (lid), Nunc GmbH & Co. KG, Wiesbaden, Germany) filled with Barth's solution (in mM: NaCl 88, KCl 1, $MgSO_4$ 0.82, $Ca(NO_3)_2$ 0.33, $CaCl_2$ 0.41, $NaHCO_3$ 2.4, Tris/HCl 5, pH7.4) and gentamicin (gentamicin sulphate, G-3632, SIGMA-ALDRICH CHEMIE GmbH, Deisenhofen, Germany; 100 U/ml). Then, the oocytes were kept in a cooling incubator (type KB 53, WTB Binder Labortechnik GmbH, Tuttlingen, Germany) at 19.2°C.

2. Injecting the oocytes

Injection electrodes of diameter 10 - 15 µm were prepared using a pipette-drawing device (type L/M-3P-A, List-electronic, Darmstadt-Eberstadt, Germany). Prior to injection, aliquots with the D-GABA B DNA or GIRK1/4 DNA were defrosted and diluted with water to a final concentration of 10 ng/µl. The DNA samples were centrifuged for 120 seconds at 3200 g (type Biofuge 13, Heraeus Instruments GmbH, Hanau, Germany). An extended PE

tube was subsequently used as transfer tube to fill the pipettes from the rear end. The injection electrodes were attached to a X,Y,Z positioning system (treatment centre EP1090, isel-automation, Eiterfeld, Germany). With the aid of a Macintosh computer, the oocytes in the microtiter plate wells were approached, and approximately 50 nl of the DNA solution were injected into the oocytes by briefly applying a pressure (0.5-3.0 bar, 3-6 seconds).

3. Electrophysiological measurements

A two-electrode voltage terminal equipped with a TURBO TEC-10CD (npi electronic GmbH, Tamm, Germany) amplifier was used to carry out the electrophysiological measurements. The micropipettes required for this purpose were drawn in two movements from aluminium silicate glass (capillary tube, Article No. 14 630 29, l=100 mm, $\varnothing_{ext.}$=1.60 mm, $\varnothing_{int.}$= 1.22 mm, Hilgenberg GmbH, Malsfeld, Germany) (Hamill et al., 1981). Current and voltage electrodes had a diameter of 1-3 µm and were filled with 1.5 M KCl and 1.5 M potassium acetate. The pipettes had a capacitance of 0.2-0.5 MW. To carry out the electrophysiological measurements, the oocytes were transferred into a small chamber which was flushed continuously with normal Rimland solution (in mM: KCl 90, $MgCl_2$ 3, HEPES 5, pH 7.2). To apply a substance, the perfusion solution was exchanged for a substance solution with the same composition and additionally the desired substance concentration. The successful expression of the D-GABA B DNA was checked after one week at a terminal potential of -60 mV. Unresponsive oocytes were discarded. All the others were used for substance testing. The data were documented by means of a YT plotter (YT plotter, Model BD 111, Kipp & Zonen Delft BV, AM Delft, Netherlands). When test substances were assayed in concentration series, these measurements were carried out on at least two different oocytes and at at least five different concentrations. The substances have been assayed directly without preincubation in the presence of GABA (gamma-amino-N-butyric acid, A2129, SIGMA-ALDRICH

CHEMIE GmbH, Deisenhofen, Germany) for their antagonism. The individual data were entered in Origin (evaluation software Microcal Origin, Microcal Software, Inc., Northampton, MA 01060-4410 USA) (Additive GmbH, Friedrichsdorf/Ts, Germany). Means, standard deviation, IC_{50} values and IC_{50} curves were calculated using Origin. These measurements were carried out at least in duplicate.

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Patent Claims

1. Polypeptide which exerts the biological activity of a GABA B receptor and which comprises an amino acid sequence which has at least 70% identity with a sequence of SEQ ID NO: 2, SEQ ID NO: 4 or SEQ ID NO: 6.

2. Polypeptide according to Claim 1, characterized in that the amino acid sequence corresponds to a sequence of SEQ ID NO: 2, SEQ ID NO: 4 or SEQ ID NO: 6.

3. Nucleic acid comprising a nucleotide sequence which encodes a polypeptide according to Claim 1.

4. Nucleic acid according to Claim 3, characterized in that it is single- or double-stranded DNA or RNA.

5. Nucleic acid according to Claim 4, characterized in that it is a fragment of genomic DNA or cDNA.

6. Nucleic acid according to Claim 3, characterized in that the nucleotide sequence corresponds to a sequence of SEQ ID NO: 1, SEQ ID NO: 3 or SEQ ID NO: 5.

7. Nucleic acid according to Claim 3, characterized in that it hybridizes under stringent conditions to the sequences of SEQ ID NO: 1, SEQ ID NO: 3 or SEQ ID NO: 5.

8. DNA construct comprising a nucleic acid according to any of Claims 3 to 7 and a heterologous promoter.

9. Vector comprising a nucleic acid according to any of Claims 3 to 7 or a DNA construct according to Claim 8.

10. A vector according to Claim 9, characterized in that the nucleic acid is operatively linked to regulatory sequences which ensure the expression of the nucleic acid in pro- or eukaryotic cells.

11. Host cell containing a nucleic acid according to any of Claims 3 to 7, a DNA construct according to Claim 8 or a vector according to Claim 9 or 10.

12. Host cell according to Claim 11, which is a prokaryotic cell, in particular E. coli.

13. Host cell according to Claim 11, which is a eukaryotic cell, in particular a mammalian or insect cell.

14. Antibody which binds specifically to a polypeptide according to Claim 1.

15. Transgenic invertebrate containing a nucleic acid according to any of Claims 3 to 7.

16. Transgenic invertebrate according to Claim 15, which is Drosophila melanogaster or Caenorhabditis elegans.

17. Transgenic progeny of an invertebrate according to Claim 15 or 16.

18. Method of generating a polypeptide according to Claim 1, comprising

(a) culturing a host cell according to any of Claims 11 to 13 under conditions which ensure the expression of the nucleic acid according to any of Claims 3 to 7, or

(b) expressing a nucleic acid according to any of Claims 3 to 7 in an in-vitro system, and

(c) obtaining the polypeptide from the cell, the culture medium or the in-vitro system.

19. Method of generating a nucleic acid according to any of Claims 3 to 7, comprising the following steps:

(a) full chemical synthesis in a manner known per se, or

(b) chemical synthesis of oligonucleotides, labelling of the oligonucleotides, hybridizing the oligonucleotides to DNA of a genomic library or cDNA library generated from insect genomic DNA or insect mRNA, respectively, selecting positive clones and isolating the hybridizing DNA from positive clones, or

(c) chemical synthesis of oligonucleotides and amplification of the target DNA by means of PCR.

20. Method of generating a transgenic invertebrate according to Claim 15 or 16, which comprises introducing a nucleic acid according to any of Claims 3 to 7 or a vector of Claim 9 or 10.

21. Method of finding new active compounds for crop protection, in particular compounds which alter the properties of polypeptides according to Claim 1, comprising the following steps:

(a) providing a host cell according to any of Claims 11 to 13,

(b) culturing the host cell in the presence of a chemical or of a sample comprising a multiplicity of chemicals, and

(c) detecting altered properties.

22. A method of finding a chemical which binds to a polypeptide according to Claim 1, comprising the following steps:

(a) contacting a polypeptide according to Claim 1 or a host cell according to any of Claims 11 to 13 with a chemical or a mixture of chemicals under conditions which permit the interaction of a chemical with the polypeptide, and

(b) determining the chemical which binds specifically to the polypeptide.

23. Method of finding a chemical which alters the expression of a polypeptide according to Claim 1, comprising the following steps:

(a) contacting a host cell according to any of Claims 11 to 13 or a transgenic invertebrate according to Claim 15 or 16 with a chemical or a mixture of chemicals,

(b) determining the concentration of the polypeptide according to Claim 1, and

(c) determining the chemical which specifically affects the expression of the polypeptide.

24. Use of a polypeptide according to Claim 1, of a nucleic acid according to any of Claims 3 to 7, of a vector according to Claim 9 or 10, of a host cell according to any of Claims 11 to 13, of an antibody according to Claim 14 or

of a transgenic invertebrate according to Claim 15 or 16 for finding new active compounds for crop protection or for finding genes which encode polypeptides which participate in the synthesis of functionally similar GABA B receptors in insects.

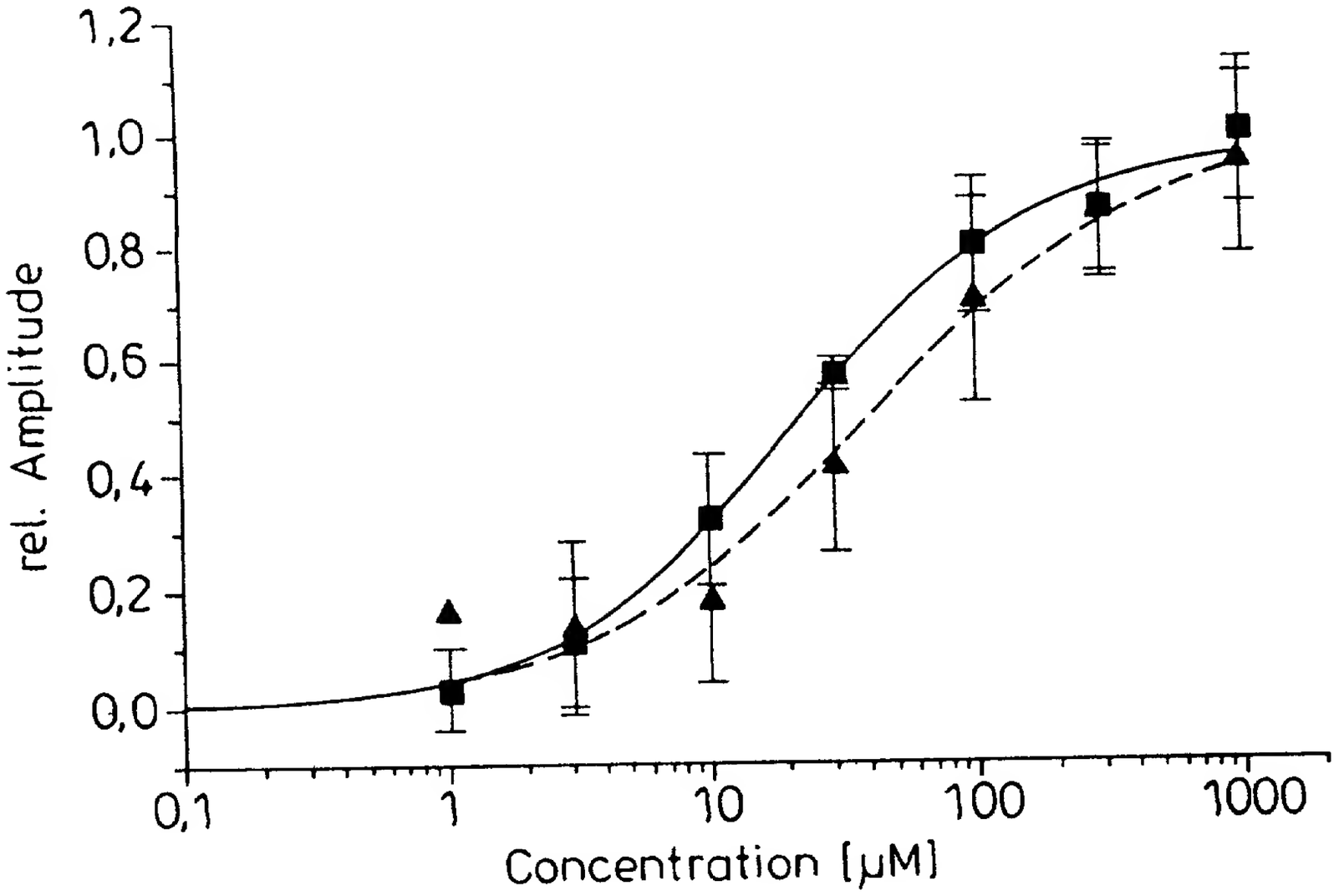
25. Use of a modulator of a polypeptide according to Claim 1 as insecticide.

GABA B Receptors

Abstract

The invention relates to polypeptides which exert the biological activity of GABA B receptors, and to nucleic acids which encode these polypeptides, and in particular to their use for finding active compounds for crop protection.

Fig. 1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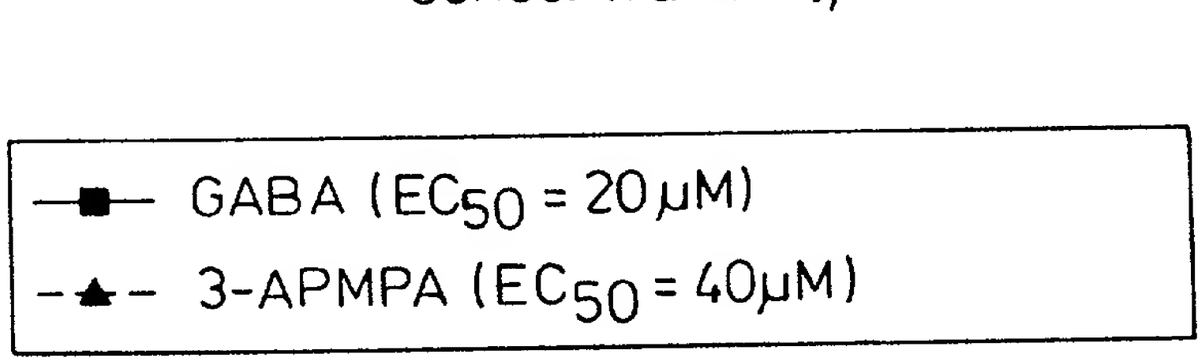
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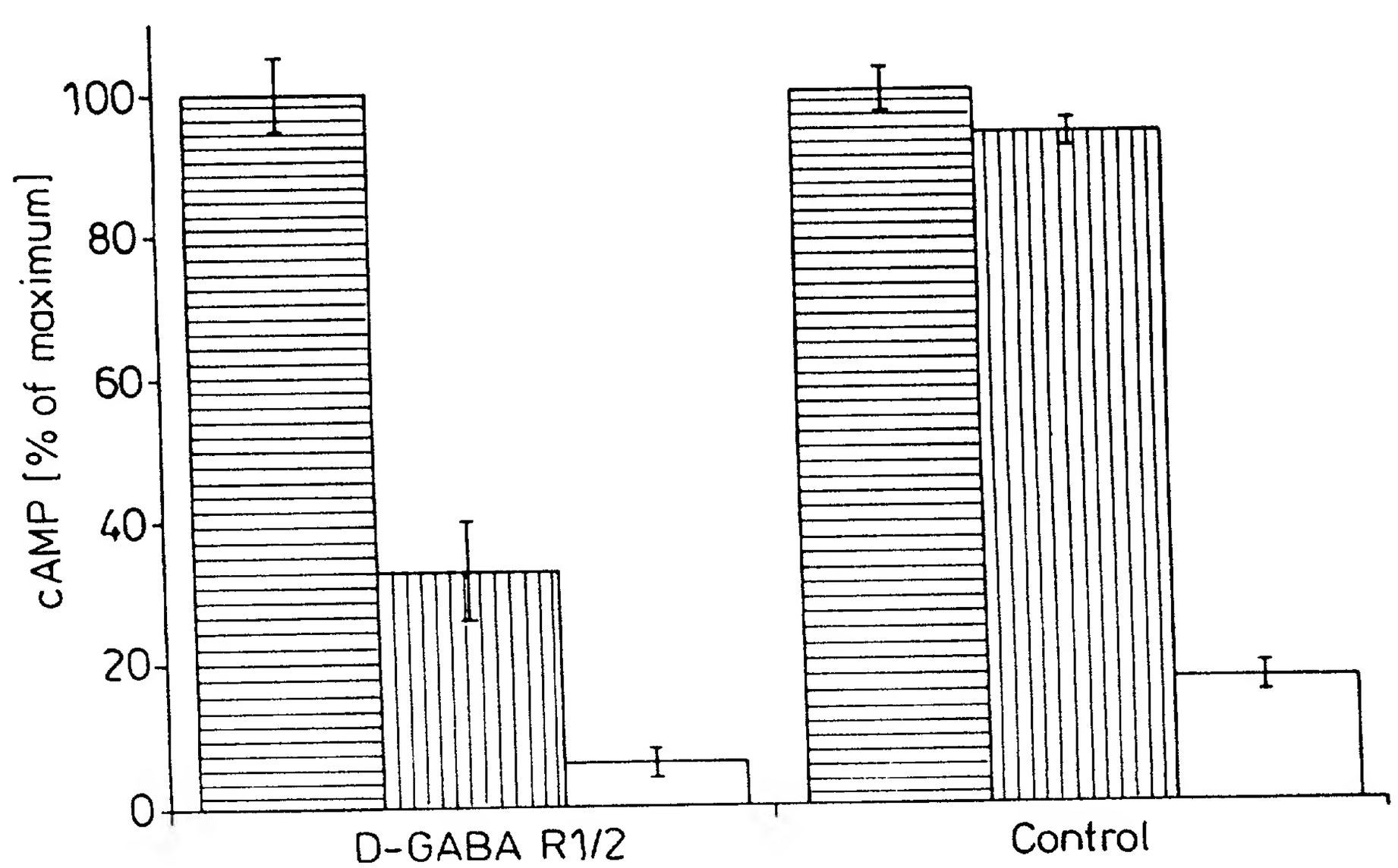
3-APMPA (EC_{50} = 40µM)

Fig. 2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40
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D-GABA R1/2
Control
forskolin
forskolin/GABA
GABA

COMBINED DECLARATION AND POWER OF ATTORNEY	ATTORNEY DOCKET NO

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name. I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

GABA B receptors

the specification of which is attached hereto,

or was filed on _____ as

Application Serial No. _____

☐ I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s), the priority(ies) of which is/are to be claimed:

19955408.0	Germany	November 18, 1999
(Number)	(Country)	(Month/Day/Year Filed)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose the material information as defined in Title 37, Code of Federal Regulations, §1.56 which occured between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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             20                  25                  30

agg ccc gat gaa ctg cac atc ggc ggc atc ttt ccg ata gcc ggc aaa   144
Arg Pro Asp Glu Leu His Ile Gly Gly Ile Phe Pro Ile Ala Gly Lys
         35                  40                  45

gga gga tgg cag ggc ggc cag gcg tgt atg cct gcc aca aga ctg gcg   192
Gly Gly Trp Gln Gly Gly Gln Ala Cys Met Pro Ala Thr Arg Leu Ala
     50                  55                  60

ttg gat gat gtc aac aag cag ccg aat ctg ctg ccg ggc ttc aag ctc   240
Leu Asp Asp Val Asn Lys Gln Pro Asn Leu Leu Pro Gly Phe Lys Leu
 65                  70                  75                  80

atc ctg cac agc aac gac agc gag tgt gag ccc ggt ttg ggc gcc agc   288
Ile Leu His Ser Asn Asp Ser Glu Cys Glu Pro Gly Leu Gly Ala Ser
                 85                  90                  95

gtg atg tac aat ctg ctc tat aat aaa ccg caa aag ctg atg ctg ttg   336
Val Met Tyr Asn Leu Leu Tyr Asn Lys Pro Gln Lys Leu Met Leu Leu
            100                 105                 110

gca gga tgc agc acg gtc tgc acc act gta gcc gag gct gcc aaa atg   384
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Ala Gly Cys Ser Thr Val Cys Thr Thr Val Ala Glu Ala Ala Lys Met
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Trp Asn Leu Ile Val Leu Cys Tyr Gly Ala Ser Ser Pro Ala Leu Ser
130 135 140

gat cgc aaa cga ttc ccc act cta ttc cgc acc cat cca tcg gcc acg 480
Asp Arg Lys Arg Phe Pro Thr Leu Phe Arg Thr His Pro Ser Ala Thr
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Val His Asn Pro Thr Arg Ile Lys Leu Met Lys Lys Phe Gly Trp Ser
165 170 175

cgg gtg gcc att ctg cag cag gcg gag gag gtc ttt ata tcg acc gta 576
Arg Val Ala Ile Leu Gln Gln Ala Glu Glu Val Phe Ile Ser Thr Val
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gag gat ctc gag aat cga tgc atg gag gct ggc gtt gaa atc gta act 624
Glu Asp Leu Glu Asn Arg Cys Met Glu Ala Gly Val Glu Ile Val Thr
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225 230 235 240

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245 250 255

cat gtg tgg ttc ttt att ggc tgg tac gag gac aac tgg tac gag gtg 816
His Val Trp Phe Phe Ile Gly Trp Tyr Glu Asp Asn Trp Tyr Glu Val
260 265 270

aat ctg aaa gca gag ggc atc acc tgc act gtt gaa cag atg cga ata 864
Asn Leu Lys Ala Glu Gly Ile Thr Cys Thr Val Glu Gln Met Arg Ile
275 280 285

gct gcc gaa gga cat ctg aca acg gaa gcg ctc atg tgg aat cag aac 912
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290 295 300

aat cag aca act ata tcc gga atg act gca gag gaa ttt cga cat cga 960
Asn Gln Thr Thr Ile Ser Gly Met Thr Ala Glu Glu Phe Arg His Arg
305 310 315 320

ctg aat cag gcg cta atc gag gag ggt tac gac att aac cac gat cgc 1008
Leu Asn Gln Ala Leu Ile Glu Glu Gly Tyr Asp Ile Asn His Asp Arg
325 330 335

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Tyr Pro Glu Gly Tyr Gln Glu Ala Pro Leu Ala Tyr Asp Ala Val Trp

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                340                 345                 350

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Ser Val Ala Leu Ala Phe Asn Lys Thr Met Glu Arg Leu Thr Thr Gly
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aag aaa tct ctg agg gat ttt acc tat acg gac aag gag att gcc gat   1152
Lys Lys Ser Leu Arg Asp Phe Thr Tyr Thr Asp Lys Glu Ile Ala Asp
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gaa atc tac gct gcc atg aac tcc aca caa ttt ctg ggt gta tcg ggt   1200
Glu Ile Tyr Ala Ala Met Asn Ser Thr Gln Phe Leu Gly Val Ser Gly
385                 390                 395                 400

gtg gtg gca ttc agt tct cag ggc gat cgt att gct ctt aca cag atc   1248
Val Val Ala Phe Ser Ser Gln Gly Asp Arg Ile Ala Leu Thr Gln Ile
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gaa cag atg ata gac ggc aag tac gag aag ttg ggt tac tac gat act   1296
Glu Gln Met Ile Asp Gly Lys Tyr Glu Lys Leu Gly Tyr Tyr Asp Thr
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cag ttg gat aac cta tcc tgg ttg aat act gaa cag tgg att ggt ggc   1344
Gln Leu Asp Asn Leu Ser Trp Leu Asn Thr Glu Gln Trp Ile Gly Gly
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aag gtt cct caa gat cgc aca att gtc acc cat gtt cta cgc acc gtg   1392
Lys Val Pro Gln Asp Arg Thr Ile Val Thr His Val Leu Arg Thr Val
    450                 455                 460

tcc ttg cca tta ttt gtg tgc atg tgc aca ata tcc agt tgt ggc ata   1440
Ser Leu Pro Leu Phe Val Cys Met Cys Thr Ile Ser Ser Cys Gly Ile
465                 470                 475                 480

ttc gtt gcc ttc gcc ttg atc atc ttt aat ata tgg aat aag cat aga   1488
Phe Val Ala Phe Ala Leu Ile Ile Phe Asn Ile Trp Asn Lys His Arg
                485                 490                 495

aga gta ata caa tcc tcg cat ccc gtt tgc aat acg atc atg tta ttt   1536
Arg Val Ile Gln Ser Ser His Pro Val Cys Asn Thr Ile Met Leu Phe
            500                 505                 510

ggt gtc atc atc tgt cta ata tct gtc atc tta ctg ggc atc gac gga   1584
Gly Val Ile Ile Cys Leu Ile Ser Val Ile Leu Leu Gly Ile Asp Gly
        515                 520                 525

cgc ttt gtc agc ccc gag gaa tat cca aag ata tgt caa gcg cgg gct   1632
Arg Phe Val Ser Pro Glu Glu Tyr Pro Lys Ile Cys Gln Ala Arg Ala
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tgg tta cta tcc acc ggt ttt aca cta gca tac ggt gct atg ttc agc   1680
Trp Leu Leu Ser Thr Gly Phe Thr Leu Ala Tyr Gly Ala Met Phe Ser
545                 550                 555                 560

aag gtc tgg cgt gtg cat cgt ttt aca aca aaa gca aaa act gac cca   1728
Lys Val Trp Arg Val His Arg Phe Thr Thr Lys Ala Lys Thr Asp Pro
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aag aaa aaa gtg gaa cct tgg aag cta tac acc atg gtt tcg ggg cta   1776
Lys Lys Lys Val Glu Pro Trp Lys Leu Tyr Thr Met Val Ser Gly Leu
            580                 585                 590

tta tca ata gat tta gtg ata tta ctc tca tgg cag atc ttt gat ccg   1824
Leu Ser Ile Asp Leu Val Ile Leu Leu Ser Trp Gln Ile Phe Asp Pro
        595                 600                 605

ctg cag cgt tat ctc gaa aca ttc cca ctc gaa gat cca gta tct act   1872
Leu Gln Arg Tyr Leu Glu Thr Phe Pro Leu Glu Asp Pro Val Ser Thr
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act gat gat att aaa ata cgt cca gag ctt gag cat tgt gaa agt caa   1920
Thr Asp Asp Ile Lys Ile Arg Pro Glu Leu Glu His Cys Glu Ser Gln
625                 630                 635                 640

cgc aac tcc atg tgg ttg ggt ctt gta tac ggc ttc aag ggg cta atc   1968
Arg Asn Ser Met Trp Leu Gly Leu Val Tyr Gly Phe Lys Gly Leu Ile
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ctg gtg ttt ggc ctc ttt ttg gcg tac gag acg cgc tcc att aaa gtg   2016
Leu Val Phe Gly Leu Phe Leu Ala Tyr Glu Thr Arg Ser Ile Lys Val
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aaa cag atc aac gat tcg cgt tat gtg ggc atg agc atc tat aac gtg   2064
Lys Gln Ile Asn Asp Ser Arg Tyr Val Gly Met Ser Ile Tyr Asn Val
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gtc gtc ctt tgc ctg ata aca gct ccg gtg ggc atg gtc att gca tcg   2112
Val Val Leu Cys Leu Ile Thr Ala Pro Val Gly Met Val Ile Ala Ser
    690                 695                 700

caa cag gac gcg tcc ttt gcc ttc gtt gct cta gct gtg ata ttc tgt   2160
Gln Gln Asp Ala Ser Phe Ala Phe Val Ala Leu Ala Val Ile Phe Cys
705                 710                 715                 720

tgt ttc cta agc atg ctg ctg ata ttt gtg cca aag gtc att gag gtt   2208
Cys Phe Leu Ser Met Leu Leu Ile Phe Val Pro Lys Val Ile Glu Val
                725                 730                 735

ata cgt cat ccc aag gat aag gcc gaa tcg aaa tac aat ccc gat tca   2256
Ile Arg His Pro Lys Asp Lys Ala Glu Ser Lys Tyr Asn Pro Asp Ser
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gcc ata tcg aaa gag gac gaa gaa cgc tat cag aaa ctt gtt acc gaa   2304
Ala Ile Ser Lys Glu Asp Glu Glu Arg Tyr Gln Lys Leu Val Thr Glu
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aac gag caa ttg caa cga tta ata aca cag aag gag gaa aag att cga   2352
Asn Glu Gln Leu Gln Arg Leu Ile Thr Gln Lys Glu Glu Lys Ile Arg
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gtc ctg cga cag cgt ctg gtg gag cgg ggc gac gcc aag ggc aca gaa   2400
Val Leu Arg Gln Arg Leu Val Glu Arg Gly Asp Ala Lys Gly Thr Glu
785                 790                 795                 800
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cag ccc gct tcc ctc atc aac tca tca gca cat gcc acg ccc gca gcc   2496
Gln Pro Ala Ser Leu Ile Asn Ser Ser Ala His Ala Thr Pro Ala Ala
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Arg Pro Asp Glu Leu His Ile Gly Gly Ile Phe Pro Ile Ala Gly Lys
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Ile Leu His Ser Asn Asp Ser Glu Cys Glu Pro Gly Leu Gly Ala Ser
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Val Met Tyr Asn Leu Leu Tyr Asn Lys Pro Gln Lys Leu Met Leu Leu
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Ala Gly Cys Ser Thr Val Cys Thr Thr Val Ala Glu Ala Ala Lys Met
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Trp Asn Leu Ile Val Leu Cys Tyr Gly Ala Ser Ser Pro Ala Leu Ser
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Asp Arg Lys Arg Phe Pro Thr Leu Phe Arg Thr His Pro Ser Ala Thr
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Val His Asn Pro Thr Arg Ile Lys Leu Met Lys Lys Phe Gly Trp Ser
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Arg Val Ala Ile Leu Gln Gln Ala Glu Glu Val Phe Ile Ser Thr Val
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Glu Asp Leu Glu Asn Arg Cys Met Glu Ala Gly Val Glu Ile Val Thr
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Arg Gln Asp Ala Arg Ile Ile Val Gly Leu Phe Tyr Val Val Ala Ala
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Arg Arg Val Leu Cys Glu Met Tyr Lys Gln Gln Leu Tyr Gly Arg Ala
245 250 255

His Val Trp Phe Phe Ile Gly Trp Tyr Glu Asp Asn Trp Tyr Glu Val
260 265 270

Asn Leu Lys Ala Glu Gly Ile Thr Cys Thr Val Glu Gln Met Arg Ile
275 280 285

Ala Ala Glu Gly His Leu Thr Thr Glu Ala Leu Met Trp Asn Gln Asn
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Asn Gln Thr Thr Ile Ser Gly Met Thr Ala Glu Glu Phe Arg His Arg
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325 330 335

Tyr Pro Glu Gly Tyr Gln Glu Ala Pro Leu Ala Tyr Asp Ala Val Trp
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Ser Val Ala Leu Ala Phe Asn Lys Thr Met Glu Arg Leu Thr Thr Gly
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Lys Lys Ser Leu Arg Asp Phe Thr Tyr Thr Asp Lys Glu Ile Ala Asp
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Glu Ile Tyr Ala Ala Met Asn Ser Thr Gln Phe Leu Gly Val Ser Gly
385 390 395 400

Val Val Ala Phe Ser Ser Gln Gly Asp Arg Ile Ala Leu Thr Gln Ile
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Glu Gln Met Ile Asp Gly Lys Tyr Glu Lys Leu Gly Tyr Tyr Asp Thr
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Gln Leu Asp Asn Leu Ser Trp Leu Asn Thr Glu Gln Trp Ile Gly Gly
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Lys Val Pro Gln Asp Arg Thr Ile Val Thr His Val Leu Arg Thr Val
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Ser Leu Pro Leu Phe Val Cys Met Cys Thr Ile Ser Ser Cys Gly Ile
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Phe Val Ala Phe Ala Leu Ile Ile Phe Asn Ile Trp Asn Lys His Arg
485 490 495

Arg Val Ile Gln Ser Ser His Pro Val Cys Asn Thr Ile Met Leu Phe
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Gly Val Ile Ile Cys Leu Ile Ser Val Ile Leu Leu Gly Ile Asp Gly
515 520 525

Arg Phe Val Ser Pro Glu Glu Tyr Pro Lys Ile Cys Gln Ala Arg Ala
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Trp Leu Leu Ser Thr Gly Phe Thr Leu Ala Tyr Gly Ala Met Phe Ser
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Lys Val Trp Arg Val His Arg Phe Thr Thr Lys Ala Lys Thr Asp Pro
565 570 575

Lys Lys Lys Val Glu Pro Trp Lys Leu Tyr Thr Met Val Ser Gly Leu
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595 600 605

Leu Gln Arg Tyr Leu Glu Thr Phe Pro Leu Glu Asp Pro Val Ser Thr
610 615 620

Thr Asp Asp Ile Lys Ile Arg Pro Glu Leu Glu His Cys Glu Ser Gln
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Arg Asn Ser Met Trp Leu Gly Leu Val Tyr Gly Phe Lys Gly Leu Ile
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Leu Val Phe Gly Leu Phe Leu Ala Tyr Glu Thr Arg Ser Ile Lys Val
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Lys Gln Ile Asn Asp Ser Arg Tyr Val Gly Met Ser Ile Tyr Asn Val
675 680 685

Val Val Leu Cys Leu Ile Thr Ala Pro Val Gly Met Val Ile Ala Ser
690 695 700

Gln Gln Asp Ala Ser Phe Ala Phe Val Ala Leu Ala Val Ile Phe Cys
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Cys Phe Leu Ser Met Leu Leu Ile Phe Val Pro Lys Val Ile Glu Val
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Ile Arg His Pro Lys Asp Lys Ala Glu Ser Lys Tyr Asn Pro Asp Ser
740 745 750

Ala Ile Ser Lys Glu Asp Glu Glu Arg Tyr Gln Lys Leu Val Thr Glu
755 760 765

Asn Glu Gln Leu Gln Arg Leu Ile Thr Gln Lys Glu Glu Lys Ile Arg
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Val Leu Arg Gln Arg Leu Val Glu Arg Gly Asp Ala Lys Gly Thr Glu
785 790 795 800

Leu Asn Gly Ala Thr Gly Val Ala Ser Ala Ala Val Ala Thr Thr Ser
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Leu Trp Ser Thr Ala Cys Gly Arg Thr Ala Lys Arg Ser Asp Val Tyr
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ata gcg gga ttc ttc ccg tac ggg gat ggc gtg gaa aac tcc tac acc 144
Ile Ala Gly Phe Phe Pro Tyr Gly Asp Gly Val Glu Asn Ser Tyr Thr
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Gly Arg Gly Val Met Pro Ser Val Lys Leu Ala Leu Gly His Val Asn
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Glu His Gly Lys Ile Leu Ala Asn Tyr Arg Leu His Met Trp Trp Asn
65 70 75 80

gac act cag tgc aat gct gct gtg ggc gta aag tcc ttc ttc gat atg 288
Asp Thr Gln Cys Asn Ala Ala Val Gly Val Lys Ser Phe Phe Asp Met
85 90 95

atg cat tcg ggt ccc aat aaa gtg atg ctc ttc ggc gct gcg tgc acc 336
Met His Ser Gly Pro Asn Lys Val Met Leu Phe Gly Ala Ala Cys Thr
100 105 110

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His Val Thr Asp Pro Ile Ala Lys Ala Ser Lys His Trp His Leu Thr
115 120 125

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Gln Leu Ser Tyr Ala Asp Thr His Pro Met Phe Thr Lys Asp Ala Phe
130 135 140

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165 170 175

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Tyr Gln Asn Glu Pro Arg Tyr Ser Leu Pro His Asn His Met Val Ala
180 185 190

gac ctg gat gcc atg gag gtc gag gtg gtg gaa acg cag agc ttc gtc 624
Asp Leu Asp Ala Met Glu Val Glu Val Val Glu Thr Gln Ser Phe Val
195 200 205

aac gat gtg gct gaa tca ttg aag aaa ctg cgc gag aag gac gtg agg 672
Asn Asp Val Ala Glu Ser Leu Lys Lys Leu Arg Glu Lys Asp Val Arg
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225 230 235 240

gag gct tat aaa ttg gat atg tat ggc aga gcc tat caa tgg ctg atc 768
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245 250 255

atg gct acc tat tcc acg gat tgg tgg aat gtc acg cag gac agc gag 816
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260 265 270

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Cys Ser Val Glu Glu Ile Ala Thr Ala Leu Glu Gly Ala Ile Leu Val
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Met Glu Lys Ile Gly Glu Tyr His Ser Gln Lys Ser His Leu Asp Leu
                405                 410                 415

agc ttg gga aaa cca gtc aaa tgg gtg ggg aaa act cct ccc aag gat   1296
Ser Leu Gly Lys Pro Val Lys Trp Val Gly Lys Thr Pro Pro Lys Asp
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Arg Thr Leu Ile Tyr Ile Glu His Ser Gln Val Asn Pro Thr Ile Tyr
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gca gct ttt ccc tat atc tgc aca gct cga gcc tgg atc ttg atg gct   1584
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545                 550                 555                 560

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att ata acc acc tgg cag att gcc gat ccc ttt tac cgc gaa act aaa   1776
Ile Ile Thr Thr Trp Gln Ile Ala Asp Pro Phe Tyr Arg Glu Thr Lys
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cag ttg gaa ccc ttg cat cac gag aat att gat gat gtc ttg gtg atc   1824
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625                 630                 635                 640

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cat att ggt ttc tcc gtt tat aac gtg ttc atc act tgt ctg gcc gga   2016
His Ile Gly Phe Ser Val Tyr Asn Val Phe Ile Thr Cys Leu Ala Gly
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gcg gct ata tcc ctg gtg cta tcg gat cga aag gat tta gtt ttt gtc   2064
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tta ctc tcg ttt ttt atc att ttt tgt acg aca gcc act ttg tgt ttg   2112
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gtg gac aaa cgc gtt agg gcc acg ttg aga ccc atg tcc aaa aac gga   2208
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atc gat ggg gtg acc tgc aca ggt ggc tcc aac gtc ggt agc gaa ctg   2400
Ile Asp Gly Val Thr Cys Thr Gly Gly Ser Asn Val Gly Ser Glu Leu
785                 790                 795                 800

gag ccc ata ctg aac gat gac att gtt agg ctc tca gct cca ccg gtg   2448
Glu Pro Ile Leu Asn Asp Asp Ile Val Arg Leu Ser Ala Pro Pro Val
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cgt cga gag atg ccc agc acc aca gtt acc gag atg acg tcc gtg gat   2496
Arg Arg Glu Met Pro Ser Thr Thr Val Thr Glu Met Thr Ser Val Asp
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Ser Val Thr Ser Thr His Val Glu Met Asp Asn Ser Phe Val Ser Val
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cag tct aca gtg atg gcg cca tcg ctt cct ccc aaa aag aaa aag caa   2592
Gln Ser Thr Val Met Ala Pro Ser Leu Pro Pro Lys Lys Lys Lys Gln
    850                 855                 860

tcg att gta gag cac cac tcg cat gcc cct gct cca act atg atg cag   2640
Ser Ile Val Glu His His Ser His Ala Pro Ala Pro Thr Met Met Gln
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ccc atc cag cag caa ctg cag cag cac tta cag caa cat cag cag atg   2688
Pro Ile Gln Gln Gln Leu Gln Gln His Leu Gln Gln His Gln Gln Met
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cag cag cag cac ctg cag cag cag caa cac cag cag atg caa cag caa   2736
Gln Gln Gln His Leu Gln Gln Gln Gln His Gln Gln Met Gln Gln Gln
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cag cag cag cag cag cat cat cat cgc cat ctg gag aag aga aac tcg   2784
Gln Gln Gln Gln Gln His His His Arg His Leu Glu Lys Arg Asn Ser
        915                 920                 925

gtg tcc gct cag acc gat gat aat ata ggc agc atc acc agt acg gcg   2832
Val Ser Ala Gln Thr Asp Asp Asn Ile Gly Ser Ile Thr Ser Thr Ala
    930                 935                 940

ggc aag cgg agc gga gga gac tgc tcc agc atg cgg gag agg cgt caa   2880
Gly Lys Arg Ser Gly Gly Asp Cys Ser Ser Met Arg Glu Arg Arg Gln
945                 950                 955                 960

tcg acc gcc tcc agg cac tac gac agt ggc agc cag acg ccc acc gcc   2928
Ser Thr Ala Ser Arg His Tyr Asp Ser Gly Ser Gln Thr Pro Thr Ala
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cgg cca aag tac agc agc tcg cac cgg aac tcc tcc acc aac atc tcc   2976
Arg Pro Lys Tyr Ser Ser Ser His Arg Asn Ser Ser Thr Asn Ile Ser
            980                 985                 990

aca tcg caa tcg gag ttg agc aac atg tgt cca cac tca aag ccc agt   3024
Thr Ser Gln Ser Glu Leu Ser Asn Met Cys Pro His Ser Lys Pro Ser
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act ccg gct gtg att aag act ccc act gcc tcc gac cat cgc cgc acc   3072
Thr Pro Ala Val Ile Lys Thr Pro Thr Ala Ser Asp His Arg Arg Thr
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agc atg ggc tcc gct ctg aag tcc aat ttc gtg gtt tca cag agt gac   3120
Ser Met Gly Ser Ala Leu Lys Ser Asn Phe Val Val Ser Gln Ser Asp
1025                1030                1035                1040

ctc tgg gac acg cac acg ctg tcg cac gcc aag cag cgc cag tcg ccg   3168
Leu Trp Asp Thr His Thr Leu Ser His Ala Lys Gln Arg Gln Ser Pro
                1045                1050                1055

cgg aac tac gcc agt ccg cag cgc tgt gcg gaa cat cat ggc ggc cac   3216
Arg Asn Tyr Ala Ser Pro Gln Arg Cys Ala Glu His His Gly Gly His
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Gly Met Thr Tyr Asp Pro Asn Thr Thr Ser Pro Ile Gln Arg Ser Val
1075 1080 1085

tcc gag aag aac cgc aac aaa cat cgg cca aaa ccg caa aag ggc acc 3312
Ser Glu Lys Asn Arg Asn Lys His Arg Pro Lys Pro Gln Lys Gly Thr
1090 1095 1100

gtt tgc cag agc gag acg gac agc gaa cgg gaa cga gat ccg ccg ccc 3360
Val Cys Gln Ser Glu Thr Asp Ser Glu Arg Glu Arg Asp Pro Pro Pro
1105 1110 1115 1120

aac agt cag ccg tgc gtc cag ccg cgt aag gtc agc cgg agc tct aac 3408
Asn Ser Gln Pro Cys Val Gln Pro Arg Lys Val Ser Arg Ser Ser Asn
1125 1130 1135

atc cag cac gcc gcc cac cac cac agt tcg ccc aat gtg gcg ccc gat 3456
Ile Gln His Ala Ala His His His Ser Ser Pro Asn Val Ala Pro Asp
1140 1145 1150

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Lys Gln Arg Ser Arg Gln Arg Gly Lys Gln Asp Ser Ser Ile Tyr Gly
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1170 1175 1180

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Ile Phe Arg Lys Leu Leu Thr Glu Lys Ser Pro Asn Tyr Arg Gly Arg
1185 1190 1195 1200

agt gcc gtg ggc cag agc tgt ccg aat ata tcc atc aaa tgc gat atc 3648
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35 40 45

Gly Arg Gly Val Met Pro Ser Val Lys Leu Ala Leu Gly His Val Asn
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Glu His Gly Lys Ile Leu Ala Asn Tyr Arg Leu His Met Trp Trp Asn
65 70 75 80

Asp Thr Gln Cys Asn Ala Ala Val Gly Val Lys Ser Phe Phe Asp Met
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Met His Ser Gly Pro Asn Lys Val Met Leu Phe Gly Ala Ala Cys Thr
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His Val Thr Asp Pro Ile Ala Lys Ala Ser Lys His Trp His Leu Thr
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Gln Leu Ser Tyr Ala Asp Thr His Pro Met Phe Thr Lys Asp Ala Phe
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Pro Asn Phe Phe Arg Val Val Pro Ser Glu Asn Ala Phe Asn Ala Pro
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Arg Leu Ala Leu Leu Lys Glu Phe Asn Trp Thr Arg Val Gly Thr Val
165 170 175

Tyr Gln Asn Glu Pro Arg Tyr Ser Leu Pro His Asn His Met Val Ala
180 185 190

Asp Leu Asp Ala Met Glu Val Glu Val Val Glu Thr Gln Ser Phe Val
195 200 205

Asn Asp Val Ala Glu Ser Leu Lys Lys Leu Arg Glu Lys Asp Val Arg
210 215 220

Ile Ile Leu Gly Asn Phe Asn Glu His Phe Ala Arg Lys Ala Phe Cys
225 230 235 240

Glu Ala Tyr Lys Leu Asp Met Tyr Gly Arg Ala Tyr Gln Trp Leu Ile
245 250 255

Met Ala Thr Tyr Ser Thr Asp Trp Trp Asn Val Thr Gln Asp Ser Glu
260 265 270

Cys Ser Val Glu Glu Ile Ala Thr Ala Leu Glu Gly Ala Ile Leu Val
275 280 285

Asp Leu Leu Pro Leu Ser Thr Ser Gly Asp Ile Thr Val Ala Gly Ile
290 295 300

Thr Ala Asp Glu Tyr Leu Val Glu Tyr Asp Arg Leu Arg Gly Thr Glu
305 310 315 320

Tyr Ser Arg Phe His Gly Tyr Thr Tyr Asp Gly Ile Trp Ala Ala Ala
325 330 335

Leu Ala Ile Gln Tyr Val Ala Glu Lys Arg Glu Asp Leu Leu Thr His
340 345 350

Phe Asp Tyr Arg Val Lys Asp Trp Glu Ser Val Phe Leu Glu Ala Leu
355 360 365

Arg Asn Thr Ser Phe Glu Gly Val Thr Gly Pro Val Arg Phe Tyr Asn
370 375 380

Asn Glu Arg Lys Ala Asn Ile Leu Ile Asn Gln Phe Gln Leu Gly Gln
385 390 395 400

Met Glu Lys Ile Gly Glu Tyr His Ser Gln Lys Ser His Leu Asp Leu
405 410 415

Ser Leu Gly Lys Pro Val Lys Trp Val Gly Lys Thr Pro Pro Lys Asp
420 425 430

Arg Thr Leu Ile Tyr Ile Glu His Ser Gln Val Asn Pro Thr Ile Tyr
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Ile Val Ser Ala Ser Ala Ser Val Ile Gly Val Ile Ile Ala Thr Val
450 455 460

Phe Leu Ala Phe Asn Ile Lys Tyr Arg Asn Gln Arg Tyr Ile Lys Met
465 470 475 480

Ser Ser Pro His Leu Asn Asn Leu Ile Ile Val Gly Cys Met Ile Thr
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Tyr Leu Ser Ile Ile Phe Leu Gly Leu Asp Thr Thr Leu Ser Ser Val
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Ala Ala Phe Pro Tyr Ile Cys Thr Ala Arg Ala Trp Ile Leu Met Ala
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Gly Phe Ser Leu Ser Phe Gly Ala Met Phe Ser Lys Thr Trp Arg Val
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His Ser Ile Phe Thr Asp Leu Lys Leu Asn Lys Lys Val Ile Lys Asp
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Tyr Gln Leu Phe Met Val Val Gly Val Leu Leu Ala Ile Asp Ile Ala
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Gln Leu Glu Pro Leu His His Glu Asn Ile Asp Asp Val Leu Val Ile
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Pro Glu Asn Glu Tyr Cys Gln Ser Glu His Met Thr Ile Phe Val Ser
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Ile Ile Tyr Ala Tyr Lys Gly Leu Leu Leu Val Phe Gly Ala Phe Leu
625 630 635 640

Ala Trp Glu Thr Arg His Val Ser Ile Pro Ala Leu Asn Asp Ser Lys
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His Ile Gly Phe Ser Val Tyr Asn Val Phe Ile Thr Cys Leu Ala Gly
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Ala Ala Ile Ser Leu Val Leu Ser Asp Arg Lys Asp Leu Val Phe Val
675 680 685

Leu Leu Ser Phe Phe Ile Ile Phe Cys Thr Thr Ala Thr Leu Cys Leu
690 695 700

Val Phe Val Pro Lys Leu Val Glu Leu Lys Arg Asn Pro Gln Gly Val
705 710 715 720

Val Asp Lys Arg Val Arg Ala Thr Leu Arg Pro Met Ser Lys Asn Gly
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Arg Arg Asp Ser Ser Val Cys Glu Leu Glu Gln Arg Leu Arg Asp Val
740 745 750

Lys Asn Thr Asn Cys Arg Phe Arg Lys Ala Leu Met Glu Lys Glu Asn
755 760 765

Glu Leu Gln Ala Leu Ile Arg Lys Leu Gly Pro Glu Ala Arg Lys Trp
770 775 780

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Glu Pro Ile Leu Asn Asp Asp Ile Val Arg Leu Ser Ala Pro Pro Val
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Arg Arg Glu Met Pro Ser Thr Thr Val Thr Glu Met Thr Ser Val Asp
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Ser Val Thr Ser Thr His Val Glu Met Asp Asn Ser Phe Val Ser Val
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Gln Ser Thr Val Met Ala Pro Ser Leu Pro Pro Lys Lys Lys Lys Gln
850 855 860

Ser Ile Val Glu His His Ser His Ala Pro Ala Pro Thr Met Met Gln
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Pro Ile Gln Gln Gln Leu Gln Gln His Leu Gln Gln His Gln Gln Met
885 890 895

Gln Gln Gln His Leu Gln Gln Gln Gln His Gln Gln Met Gln Gln Gln
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Gln Gln Gln Gln Gln His His His Arg His Leu Glu Lys Arg Asn Ser
915 920 925

Val Ser Ala Gln Thr Asp Asp Asn Ile Gly Ser Ile Thr Ser Thr Ala
930 935 940

Gly Lys Arg Ser Gly Gly Asp Cys Ser Ser Met Arg Glu Arg Arg Gln
945 950 955 960

Ser Thr Ala Ser Arg His Tyr Asp Ser Gly Ser Gln Thr Pro Thr Ala
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Arg Pro Lys Tyr Ser Ser Ser His Arg Asn Ser Ser Thr Asn Ile Ser
980 985 990

Thr Ser Gln Ser Glu Leu Ser Asn Met Cys Pro His Ser Lys Pro Ser
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Thr Pro Ala Val Ile Lys Thr Pro Thr Ala Ser Asp His Arg Arg Thr
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Ser Met Gly Ser Ala Leu Lys Ser Asn Phe Val Val Ser Gln Ser Asp
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Leu Trp Asp Thr His Thr Leu Ser His Ala Lys Gln Arg Gln Ser Pro
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Gly Met Thr Tyr Asp Pro Asn Thr Thr Ser Pro Ile Gln Arg Ser Val
1075 1080 1085

Ser Glu Lys Asn Arg Asn Lys His Arg Pro Lys Pro Gln Lys Gly Thr
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Val Cys Gln Ser Glu Thr Asp Ser Glu Arg Glu Arg Asp Pro Pro Pro
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Asn Ser Gln Pro Cys Val Gln Pro Arg Lys Val Ser Arg Ser Ser Asn
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Ile Gln His Ala Ala His His His Ser Ser Pro Asn Val Ala Pro Asp
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Lys Gln Arg Ser Arg Gln Arg Gly Lys Gln Asp Ser Ser Ile Tyr Gly
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Ala Ser Ser Glu Thr Glu Leu Leu Glu Gly Glu Thr Ala Ile Leu Pro
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Ile Phe Arg Lys Leu Leu Thr Glu Lys Ser Pro Asn Tyr Arg Gly Arg
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gcc gtg gga ctg agg cta gtc ctg gcc ctt gcc tgg gca acg tcg gca    96
Ala Val Gly Leu Arg Leu Val Leu Ala Leu Ala Trp Ala Thr Ser Ala
             20                  25                  30

gcg gct gcc atg gag tca tca gcc gag ctg cag gcc ctg ggc cac gag   144
Ala Ala Ala Met Glu Ser Ser Ala Glu Leu Gln Ala Leu Gly His Glu
         35                  40                  45

gca att agg cca ggt gct gcc tca att agc aca tcc agc cca tcc agc   192
Ala Ile Arg Pro Gly Ala Ala Ser Ile Ser Thr Ser Ser Pro Ser Ser
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tcg cca ccc gga gaa tcg gca tcg act gtg act gca ggg ggg act ccg   240
Ser Pro Pro Gly Glu Ser Ala Ser Thr Val Thr Ala Gly Gly Thr Pro
 65                  70                  75                  80

att cca ccg cgc tcc gat tgg aag tac aaa cgg acg aaa gtc aaa cgc   288
Ile Pro Pro Arg Ser Asp Trp Lys Tyr Lys Arg Thr Lys Val Lys Arg
                 85                  90                  95

cgg cag cag cgc ctc aat tcg cac agc aat ctg ccc gga agc acc aat   336
Arg Gln Gln Arg Leu Asn Ser His Ser Asn Leu Pro Gly Ser Thr Asn
            100                 105                 110

gcc tcc cac gct cac cac ctc ctc aat ctg ccc ccc agg cag cga tac   384
Ala Ser His Ala His His Leu Leu Asn Leu Pro Pro Arg Gln Arg Tyr
        115                 120                 125

ttg aag gtc aac cag gtg ttc gaa agc gaa cgc cgc atg tcg ccg gcc   432
Leu Lys Val Asn Gln Val Phe Glu Ser Glu Arg Arg Met Ser Pro Ala
    130                 135                 140

gaa atg cag cgc aat cat ggc aaa atc gtg ctg ctc gga ctc ttt gag   480
Glu Met Gln Arg Asn His Gly Lys Ile Val Leu Leu Gly Leu Phe Glu
145                 150                 155                 160

ctg tcc aca tcg cgg gga cca cgt ccg gat ggt ctg agc gaa ttg gga   528
Leu Ser Thr Ser Arg Gly Pro Arg Pro Asp Gly Leu Ser Glu Leu Gly
                165                 170                 175

gct gcc acc atg gcc gtg gaa cac atc aac cgc aag cgc ctg ctg ccg   576
Ala Ala Thr Met Ala Val Glu His Ile Asn Arg Lys Arg Leu Leu Pro
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ggc tac acc ctc gag ctc gtg acc aac gat act cag tgt gat cct gga   624
Gly Tyr Thr Leu Glu Leu Val Thr Asn Asp Thr Gln Cys Asp Pro Gly
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Val Gly Val Asp Arg Phe Phe His Ala Ile Tyr Thr Gln Pro Ser Thr
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agg atg gtg atg ctg ctg gga tcg gcc tgc tcg gag gtc acc gag agc 720
Arg Met Val Met Leu Leu Gly Ser Ala Cys Ser Glu Val Thr Glu Ser
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ctg gcg aag gtg gtg ccc tac tgg aac atc gtg cag gta tcc ttc ggt 768
Leu Ala Lys Val Val Pro Tyr Trp Asn Ile Val Gln Val Ser Phe Gly
245 250 255

tcc aca tcg ccg gcg ttg agc gac agg cgg gag ttc ccc tac ttc tac 816
Ser Thr Ser Pro Ala Leu Ser Asp Arg Arg Glu Phe Pro Tyr Phe Tyr
260 265 270

agg aca gtg gcc ccg gac tcc tca cac aat ccg gcg cgc atc gct ttc 864
Arg Thr Val Ala Pro Asp Ser Ser His Asn Pro Ala Arg Ile Ala Phe
275 280 285

att cgg aag ttt ggc tgg ggc acg gtg acc act ttc tcg cag aac gag 912
Ile Arg Lys Phe Gly Trp Gly Thr Val Thr Thr Phe Ser Gln Asn Glu
290 295 300

gag gtt cac tcg ctg gcg gtg aac aac ctg gtc acc gaa ctg gag gcg 960
Glu Val His Ser Leu Ala Val Asn Asn Leu Val Thr Glu Leu Glu Ala
305 310 315 320

gcc aac ata tcc tgt gcc gcc acc atc acc ttt gcg gcc acc gac ttc 1008
Ala Asn Ile Ser Cys Ala Ala Thr Ile Thr Phe Ala Ala Thr Asp Phe
325 330 335

aag gag cag ctg ctg cta ctt agg gag acg gac acg cgc atc atc atc 1056
Lys Glu Gln Leu Leu Leu Leu Arg Glu Thr Asp Thr Arg Ile Ile Ile
340 345 350

ggc agc ttc tcg cag gag ctg gcc ccc cag atc ctg tgc gag gcc tac 1104
Gly Ser Phe Ser Gln Glu Leu Ala Pro Gln Ile Leu Cys Glu Ala Tyr
355 360 365

agg ctt cga atg ttc ggg gcg gac tac gcc tgg atc ctc cac gag agc 1152
Arg Leu Arg Met Phe Gly Ala Asp Tyr Ala Trp Ile Leu His Glu Ser
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385 390 395 400

gaa ctg cag ctg gcc gtc gag aac ctc atc gtg gtc tca acg cac aac 1248
Glu Leu Gln Leu Ala Val Glu Asn Leu Ile Val Val Ser Thr His Asn
405 410 415

agc atc gtt gga aat aac gtc agc tat agt gga ctg aac aat cac atg 1296
Ser Ile Val Gly Asn Asn Val Ser Tyr Ser Gly Leu Asn Asn His Met
420 425 430

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ttc aac tcc cag ctg cgc aag caa tcc gcc cag ttc cac ggc cag gat   1344
Phe Asn Ser Gln Leu Arg Lys Gln Ser Ala Gln Phe His Gly Gln Asp
        435                 440                 445

gga ttt ggc tcc ggt tat ggt ccc agg atc agt atc gct gca acg caa   1392
Gly Phe Gly Ser Gly Tyr Gly Pro Arg Ile Ser Ile Ala Ala Thr Gln
    450                 455                 460

tct gac tct cgt cgg cgg agg aga agg ggc gtg gta ggc acc agc gga   1440
Ser Asp Ser Arg Arg Arg Arg Arg Arg Gly Val Val Gly Thr Ser Gly
465                 470                 475                 480

ggg cac ctc ttt ccg gag gcg atc tcg cag tac gcg ccg caa acc tac   1488
Gly His Leu Phe Pro Glu Ala Ile Ser Gln Tyr Ala Pro Gln Thr Tyr
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gac gcc gtg tgg gcc atc gcc ctg gcc ttg aga gcc gct gag gag cac   1536
Asp Ala Val Trp Ala Ile Ala Leu Ala Leu Arg Ala Ala Glu Glu His
            500                 505                 510

tgg cgg cgg aac gag gag cag tcg aag ctg gac gga ttc gat tac acc   1584
Trp Arg Arg Asn Glu Glu Gln Ser Lys Leu Asp Gly Phe Asp Tyr Thr
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cgc agc gac atg gcc tgg gag ttc ctg cag caa atg ggc aag ctc cac   1632
Arg Ser Asp Met Ala Trp Glu Phe Leu Gln Gln Met Gly Lys Leu His
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ttc ctg gga gtg tcg ggc ccc gtt tcc ttc agc ggc cca gat cgc gtt   1680
Phe Leu Gly Val Ser Gly Pro Val Ser Phe Ser Gly Pro Asp Arg Val
545                 550                 555                 560

ggc acc act gcc ttc tat caa atc cag cgc ggt ttg ctg gaa ccg gtg   1728
Gly Thr Thr Ala Phe Tyr Gln Ile Gln Arg Gly Leu Leu Glu Pro Val
                565                 570                 575

gcc ctc tac tat ccg gcc acg gat gcc ctg gac ttc cgg tgt ccc cgc   1776
Ala Leu Tyr Tyr Pro Ala Thr Asp Ala Leu Asp Phe Arg Cys Pro Arg
            580                 585                 590

tgc cgg ccg gtg aag tgg cac agc ggg cag gta ccc atc gcc aag cgg   1824
Cys Arg Pro Val Lys Trp His Ser Gly Gln Val Pro Ile Ala Lys Arg
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gtg ttc aag ctg cgg gtg gcg acc atc gct cca ctg gcc ttc tac acc   1872
Val Phe Lys Leu Arg Val Ala Thr Ile Ala Pro Leu Ala Phe Tyr Thr
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atc gcc acc ctc tcc agc gtg gga atc gct ctg gcc atc acc ttc ctg   1920
Ile Ala Thr Leu Ser Ser Val Gly Ile Ala Leu Ala Ile Thr Phe Leu
625                 630                 635                 640

gcg ttc aat ctg cac ttt cgg aag ctg aag gca att aaa ctt tcc agc   1968
Ala Phe Asn Leu His Phe Arg Lys Leu Lys Ala Ile Lys Leu Ser Ser
                645                 650                 655
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ccg aag ctg agc aac atc acc gca gtg ggc tgc atc ttt gtg tac gcc   2016
Pro Lys Leu Ser Asn Ile Thr Ala Val Gly Cys Ile Phe Val Tyr Ala
            660                 665                 670

acc gtc atc ctt ttg ggc ttg gac cac tcg acg ctg ccc tcg gcg gag   2064
Thr Val Ile Leu Leu Gly Leu Asp His Ser Thr Leu Pro Ser Ala Glu
        675                 680                 685

gac tct ttc gca acg gtc tgc acg gcc cgc gtc tat ctg ctc tcc gcc   2112
Asp Ser Phe Ala Thr Val Cys Thr Ala Arg Val Tyr Leu Leu Ser Ala
    690                 695                 700

gga ttc tcg ttg gcc ttt gga tcg atg ttt gcc aag acc tac aga gtg   2160
Gly Phe Ser Leu Ala Phe Gly Ser Met Phe Ala Lys Thr Tyr Arg Val
705                 710                 715                 720

cat cgg ata ttc act cgt acc ggc agc gtt ttc aag gac aag atg ctg   2208
His Arg Ile Phe Thr Arg Thr Gly Ser Val Phe Lys Asp Lys Met Leu
                725                 730                 735

cag gac att caa ctg atc ttg ctc gtc ggc gga ttg ctt ctg gtg gat   2256
Gln Asp Ile Gln Leu Ile Leu Leu Val Gly Gly Leu Leu Leu Val Asp
            740                 745                 750

gcg ctg ctc gta acc ctt tgg gtg gtc acc gat cca atg gag cgc cat   2304
Ala Leu Leu Val Thr Leu Trp Val Val Thr Asp Pro Met Glu Arg His
        755                 760                 765

ctt cac aac ctg acg ctc gag atc agt gcg act gat aga agt gtc gtt   2352
Leu His Asn Leu Thr Leu Glu Ile Ser Ala Thr Asp Arg Ser Val Val
    770                 775                 780

tac cag cct cag gtt gaa gtt tgc cgt tcg cag cac acg caa acg tgg   2400
Tyr Gln Pro Gln Val Glu Val Cys Arg Ser Gln His Thr Gln Thr Trp
785                 790                 795                 800

ttg agt gtc ctg tac gcc tac aaa ggc ctt ctt ctt gtg gtg ggt gtc   2448
Leu Ser Val Leu Tyr Ala Tyr Lys Gly Leu Leu Leu Val Val Gly Val
                805                 810                 815

tat atg gcc tgg gag acg cgc cac gta aaa ata cct gct ctc aat gac   2496
Tyr Met Ala Trp Glu Thr Arg His Val Lys Ile Pro Ala Leu Asn Asp
            820                 825                 830

tcg cag tac atc gga gtg tct gta tac agt gtg gtc atc acc agc gcc   2544
Ser Gln Tyr Ile Gly Val Ser Val Tyr Ser Val Val Ile Thr Ser Ala
        835                 840                 845

atc gtc gtg gtg ctg gcc aac ttg att tcg gag cga gtc acc ctg gcc   2592
Ile Val Val Val Leu Ala Asn Leu Ile Ser Glu Arg Val Thr Leu Ala
    850                 855                 860

ttc atc aca atc aca gct ctg att tta acc agc acc act gca acc ctt   2640
Phe Ile Thr Ile Thr Ala Leu Ile Leu Thr Ser Thr Thr Ala Thr Leu
865                 870                 875                 880

tgt ctg ctt ttc atc cca aaa ctc cat gat att tgg gca aga aac gat   2688
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Cys Leu Leu Phe Ile Pro Lys Leu His Asp Ile Trp Ala Arg Asn Asp
                885                 890                 895

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Ile Ile Asp Pro Val Ile His Ser Met Gly Leu Lys Met Glu Cys Asn
            900                 905                 910

aca cgc cga ttc gtg gtc gat gat cgc cga gaa ctg cag tat cga gtg   2784
Thr Arg Arg Phe Val Val Asp Asp Arg Arg Glu Leu Gln Tyr Arg Val
        915                 920                 925

gag gtg caa aac agg gtc tat aag aag gaa atc cag gct ctg gac gcc   2832
Glu Val Gln Asn Arg Val Tyr Lys Lys Glu Ile Gln Ala Leu Asp Ala
    930                 935                 940

gag att cga aag ctg gag agg cta ctc gag tcg gga cta acc acc acc   2880
Glu Ile Arg Lys Leu Glu Arg Leu Leu Glu Ser Gly Leu Thr Thr Thr
945                 950                 955                 960

tcc acc aca act tcg tcg tcc aca tca ctc tta act ggg gga ggt cat   2928
Ser Thr Thr Thr Ser Ser Ser Thr Ser Leu Leu Thr Gly Gly Gly His
                965                 970                 975

cta aag cca gaa ctg acg gta acc agt ggc atc tcg cag act ccg gct   2976
Leu Lys Pro Glu Leu Thr Val Thr Ser Gly Ile Ser Gln Thr Pro Ala
            980                 985                 990

gca agt aaa aac aga act cca agt atc tcg gga ata ctg ccc aat ctc   3024
Ala Ser Lys Asn Arg Thr Pro Ser Ile Ser Gly Ile Leu Pro Asn Leu
        995                1000                1005

ctg ctt tcc gtg ctg cct cct gtg att cca cgg gcc agt tgg ccg tca   3072
Leu Leu Ser Val Leu Pro Pro Val Ile Pro Arg Ala Ser Trp Pro Ser
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gca gag tac atg cag atc ccg atg agg cgt tct gtt acc ttt gcc tcc   3120
Ala Glu Tyr Met Gln Ile Pro Met Arg Arg Ser Val Thr Phe Ala Ser
1025                1030                1035                1040

cag ccc caa tta gag gag gcc tgc ctg cct gca cag gac ttg att aac   3168
Gln Pro Gln Leu Glu Glu Ala Cys Leu Pro Ala Gln Asp Leu Ile Asn
                1045                1050                1055

ctc cgt tta gcc cac cag cag gcc acg gag gct aag acg ggc ttg ata   3216
Leu Arg Leu Ala His Gln Gln Ala Thr Glu Ala Lys Thr Gly Leu Ile
            1060                1065                1070

aac cga tta cga ggg ata ttt tct cgc acc act tcg agc aac aag gga   3264
Asn Arg Leu Arg Gly Ile Phe Ser Arg Thr Thr Ser Ser Asn Lys Gly
        1075                1080                1085

tcc acc gcc agc ttg gcg gac caa aag ggt ctg aag gcg gcc ttt aaa   3312
Ser Thr Ala Ser Leu Ala Asp Gln Lys Gly Leu Lys Ala Ala Phe Lys
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tcg cac atg gga ctg ttc acc cgc ctg att ccc tcc tct caa acg gcg   3360
Ser His Met Gly Leu Phe Thr Arg Leu Ile Pro Ser Ser Gln Thr Ala
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1105                1110                1115                1120

tcc tgc aat gcc ata tac aat aat cca aat cag gat tcc att ccc tca   3408
Ser Cys Asn Ala Ile Tyr Asn Asn Pro Asn Gln Asp Ser Ile Pro Ser
                1125                1130                1135

gag gcg tcc tcc cac ccg aat ggt aac cac cta aag ccc atc cat agg   3456
Glu Ala Ser Ser His Pro Asn Gly Asn His Leu Lys Pro Ile His Arg
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ggt tca ttg acc aaa agc ggt act cac ctg gat cac ctt acc aag gat   3504
Gly Ser Leu Thr Lys Ser Gly Thr His Leu Asp His Leu Thr Lys Asp
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ccg aat ttc ctg cct atc ccc act att tct ggc ggt gaa cag ggg gac   3552
Pro Asn Phe Leu Pro Ile Pro Thr Ile Ser Gly Gly Glu Gln Gly Asp
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caa acg ttg ggt gga aag tat gtg aaa ctg ctg gag acc aag gtg aac   3600
Gln Thr Leu Gly Gly Lys Tyr Val Lys Leu Leu Glu Thr Lys Val Asn
1185                1190                1195                1200

ttc caa ttg ccc agc aac cgg aga cct tcg gtg gtg cag cag cca ccc   3648
Phe Gln Leu Pro Ser Asn Arg Arg Pro Ser Val Val Gln Gln Pro Pro
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agt tta agg gaa agg gta agg ggt tcg cca cgc ttt cca cac cgc atc   3696
Ser Leu Arg Glu Arg Val Arg Gly Ser Pro Arg Phe Pro His Arg Ile
            1220                1225                1230

ctg ccg ccc act tgc agt ctc agc gcc ctg gcc gaa tcc gag gac cgt   3744
Leu Pro Pro Thr Cys Ser Leu Ser Ala Leu Ala Glu Ser Glu Asp Arg
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ccc gga gat agc acc tct atc ttg ggc agc tgc aag tcc ata cct cgc   3792
Pro Gly Asp Ser Thr Ser Ile Leu Gly Ser Cys Lys Ser Ile Pro Arg
    1250                1255                1260

att tcg ctg cag cag gtc acc agt gga ggc acc tgg aaa tcg atg gaa   3840
Ile Ser Leu Gln Gln Val Thr Ser Gly Gly Thr Trp Lys Ser Met Glu
1265                1270                1275                1280

aca gtg ggc aag tcg agg ctt tcc ctc ggc gat tcc cag gaa gag gag   3888
Thr Val Gly Lys Ser Arg Leu Ser Leu Gly Asp Ser Gln Glu Glu Glu
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Gln Gln Ala Pro Ala Asn Gly Thr Glu
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<213> Drosophila melanogaster

<400> 6

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Ala Ala Ala Met Glu Ser Ser Ala Glu Leu Gln Ala Leu Gly His Glu
35 40 45

Ala Ile Arg Pro Gly Ala Ala Ser Ile Ser Thr Ser Ser Pro Ser Ser
50 55 60

Ser Pro Pro Gly Glu Ser Ala Ser Thr Val Thr Ala Gly Gly Thr Pro
65 70 75 80

Ile Pro Pro Arg Ser Asp Trp Lys Tyr Lys Arg Thr Lys Val Lys Arg
85 90 95

Arg Gln Gln Arg Leu Asn Ser His Ser Asn Leu Pro Gly Ser Thr Asn
100 105 110

Ala Ser His Ala His His Leu Leu Asn Leu Pro Pro Arg Gln Arg Tyr
115 120 125

Leu Lys Val Asn Gln Val Phe Glu Ser Glu Arg Arg Met Ser Pro Ala
130 135 140

Glu Met Gln Arg Asn His Gly Lys Ile Val Leu Leu Gly Leu Phe Glu
145 150 155 160

Leu Ser Thr Ser Arg Gly Pro Arg Pro Asp Gly Leu Ser Glu Leu Gly
165 170 175

Ala Ala Thr Met Ala Val Glu His Ile Asn Arg Lys Arg Leu Leu Pro
180 185 190

Gly Tyr Thr Leu Glu Leu Val Thr Asn Asp Thr Gln Cys Asp Pro Gly
195 200 205

Val Gly Val Asp Arg Phe Phe His Ala Ile Tyr Thr Gln Pro Ser Thr
210 215 220

Arg Met Val Met Leu Leu Gly Ser Ala Cys Ser Glu Val Thr Glu Ser
225 230 235 240

Leu Ala Lys Val Val Pro Tyr Trp Asn Ile Val Gln Val Ser Phe Gly
245 250 255

Ser Thr Ser Pro Ala Leu Ser Asp Arg Arg Glu Phe Pro Tyr Phe Tyr
260 265 270

Arg Thr Val Ala Pro Asp Ser Ser His Asn Pro Ala Arg Ile Ala Phe
275 280 285

Ile Arg Lys Phe Gly Trp Gly Thr Val Thr Thr Phe Ser Gln Asn Glu
290 295 300

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Glu Val His Ser Leu Ala Val Asn Asn Leu Val Thr Glu Leu Glu Ala
305                 310                 315                 320

Ala Asn Ile Ser Cys Ala Ala Thr Ile Thr Phe Ala Ala Thr Asp Phe
                325                 330                 335

Lys Glu Gln Leu Leu Leu Leu Arg Glu Thr Asp Thr Arg Ile Ile Ile
            340                 345                 350

Gly Ser Phe Ser Gln Glu Leu Ala Pro Gln Ile Leu Cys Glu Ala Tyr
        355                 360                 365

Arg Leu Arg Met Phe Gly Ala Asp Tyr Ala Trp Ile Leu His Glu Ser
    370                 375                 380

Met Gly Ala Pro Trp Trp Pro Asp Gln Arg Thr Ala Cys Ser Asn His
385                 390                 395                 400

Glu Leu Gln Leu Ala Val Glu Asn Leu Ile Val Val Ser Thr His Asn
                405                 410                 415

Ser Ile Val Gly Asn Asn Val Ser Tyr Ser Gly Leu Asn Asn His Met
            420                 425                 430

Phe Asn Ser Gln Leu Arg Lys Gln Ser Ala Gln Phe His Gly Gln Asp
        435                 440                 445

Gly Phe Gly Ser Gly Tyr Gly Pro Arg Ile Ser Ile Ala Ala Thr Gln
    450                 455                 460

Ser Asp Ser Arg Arg Arg Arg Arg Arg Gly Val Val Gly Thr Ser Gly
465                 470                 475                 480

Gly His Leu Phe Pro Glu Ala Ile Ser Gln Tyr Ala Pro Gln Thr Tyr
                485                 490                 495

Asp Ala Val Trp Ala Ile Ala Leu Ala Leu Arg Ala Ala Glu Glu His
            500                 505                 510

Trp Arg Arg Asn Glu Glu Gln Ser Lys Leu Asp Gly Phe Asp Tyr Thr
        515                 520                 525

Arg Ser Asp Met Ala Trp Glu Phe Leu Gln Gln Met Gly Lys Leu His
    530                 535                 540

Phe Leu Gly Val Ser Gly Pro Val Ser Phe Ser Gly Pro Asp Arg Val
545                 550                 555                 560

Gly Thr Thr Ala Phe Tyr Gln Ile Gln Arg Gly Leu Leu Glu Pro Val
                565                 570                 575

Ala Leu Tyr Tyr Pro Ala Thr Asp Ala Leu Asp Phe Arg Cys Pro Arg
            580                 585                 590

Cys Arg Pro Val Lys Trp His Ser Gly Gln Val Pro Ile Ala Lys Arg
        595                 600                 605
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Val Phe Lys Leu Arg Val Ala Thr Ile Ala Pro Leu Ala Phe Tyr Thr
610 615 620

Ile Ala Thr Leu Ser Ser Val Gly Ile Ala Leu Ala Ile Thr Phe Leu
625 630 635 640

Ala Phe Asn Leu His Phe Arg Lys Leu Lys Ala Ile Lys Leu Ser Ser
645 650 655

Pro Lys Leu Ser Asn Ile Thr Ala Val Gly Cys Ile Phe Val Tyr Ala
660 665 670

Thr Val Ile Leu Leu Gly Leu Asp His Ser Thr Leu Pro Ser Ala Glu
675 680 685

Asp Ser Phe Ala Thr Val Cys Thr Ala Arg Val Tyr Leu Leu Ser Ala
690 695 700

Gly Phe Ser Leu Ala Phe Gly Ser Met Phe Ala Lys Thr Tyr Arg Val
705 710 715 720

His Arg Ile Phe Thr Arg Thr Gly Ser Val Phe Lys Asp Lys Met Leu
725 730 735

Gln Asp Ile Gln Leu Ile Leu Leu Val Gly Gly Leu Leu Leu Val Asp
740 745 750

Ala Leu Leu Val Thr Leu Trp Val Val Thr Asp Pro Met Glu Arg His
755 760 765

Leu His Asn Leu Thr Leu Glu Ile Ser Ala Thr Asp Arg Ser Val Val
770 775 780

Tyr Gln Pro Gln Val Glu Val Cys Arg Ser Gln His Thr Gln Thr Trp
785 790 795 800

Leu Ser Val Leu Tyr Ala Tyr Lys Gly Leu Leu Leu Val Val Gly Val
805 810 815

Tyr Met Ala Trp Glu Thr Arg His Val Lys Ile Pro Ala Leu Asn Asp
820 825 830

Ser Gln Tyr Ile Gly Val Ser Val Tyr Ser Val Val Ile Thr Ser Ala
835 840 845

Ile Val Val Val Leu Ala Asn Leu Ile Ser Glu Arg Val Thr Leu Ala
850 855 860

Phe Ile Thr Ile Thr Ala Leu Ile Leu Thr Ser Thr Thr Ala Thr Leu
865 870 875 880

Cys Leu Leu Phe Ile Pro Lys Leu His Asp Ile Trp Ala Arg Asn Asp
885 890 895

Ile Ile Asp Pro Val Ile His Ser Met Gly Leu Lys Met Glu Cys Asn
900 905 910

Thr Arg Arg Phe Val Val Asp Asp Arg Arg Glu Leu Gln Tyr Arg Val
915 920 925

Glu Val Gln Asn Arg Val Tyr Lys Lys Glu Ile Gln Ala Leu Asp Ala
930 935 940

Glu Ile Arg Lys Leu Glu Arg Leu Leu Glu Ser Gly Leu Thr Thr Thr
945 950 955 960

Ser Thr Thr Thr Ser Ser Ser Thr Ser Leu Leu Thr Gly Gly Gly His
965 970 975

Leu Lys Pro Glu Leu Thr Val Thr Ser Gly Ile Ser Gln Thr Pro Ala
980 985 990

Ala Ser Lys Asn Arg Thr Pro Ser Ile Ser Gly Ile Leu Pro Asn Leu
995 1000 1005

Leu Leu Ser Val Leu Pro Pro Val Ile Pro Arg Ala Ser Trp Pro Ser
1010 1015 1020

Ala Glu Tyr Met Gln Ile Pro Met Arg Arg Ser Val Thr Phe Ala Ser
025 1030 1035 1040

Gln Pro Gln Leu Glu Glu Ala Cys Leu Pro Ala Gln Asp Leu Ile Asn
1045 1050 1055

Leu Arg Leu Ala His Gln Gln Ala Thr Glu Ala Lys Thr Gly Leu Ile
1060 1065 1070

Asn Arg Leu Arg Gly Ile Phe Ser Arg Thr Thr Ser Ser Asn Lys Gly
1075 1080 1085

Ser Thr Ala Ser Leu Ala Asp Gln Lys Gly Leu Lys Ala Ala Phe Lys
1090 1095 1100

Ser His Met Gly Leu Phe Thr Arg Leu Ile Pro Ser Ser Gln Thr Ala
105 1110 1115 1120

Ser Cys Asn Ala Ile Tyr Asn Asn Pro Asn Gln Asp Ser Ile Pro Ser
1125 1130 1135

Glu Ala Ser Ser His Pro Asn Gly Asn His Leu Lys Pro Ile His Arg
1140 1145 1150

Gly Ser Leu Thr Lys Ser Gly Thr His Leu Asp His Leu Thr Lys Asp
1155 1160 1165

Pro Asn Phe Leu Pro Ile Pro Thr Ile Ser Gly Gly Glu Gln Gly Asp
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Gln Thr Leu Gly Gly Lys Tyr Val Lys Leu Leu Glu Thr Lys Val Asn
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Phe Gln Leu Pro Ser Asn Arg Arg Pro Ser Val Val Gln Gln Pro Pro
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Ser Leu Arg Glu Arg Val Arg Gly Ser Pro Arg Phe Pro His Arg Ile
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Leu Pro Pro Thr Cys Ser Leu Ser Ala Leu Ala Glu Ser Glu Asp Arg
1235 1240 1245

Pro Gly Asp Ser Thr Ser Ile Leu Gly Ser Cys Lys Ser Ile Pro Arg
1250 1255 1260

Ile Ser Leu Gln Gln Val Thr Ser Gly Gly Thr Trp Lys Ser Met Glu
265 1270 1275 1280

Thr Val Gly Lys Ser Arg Leu Ser Leu Gly Asp Ser Gln Glu Glu Glu
1285 1290 1295

Gln Gln Ala Pro Ala Asn Gly Thr Glu
1300 1305